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## ORIGINAL ARTICLES

# PENICILLIN IN THE TREATMENT OF PNEUMOCOCCAL, MENINGOCOCCAL, STREPTOCOCCAL AND STAPHYLOCOCCAL MENINGITIS*

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The effect of penicillin in 71 cases of acute coccal meningitis has been studied and an evaluation attempted both in terms of gross mortality figures and in terms of clinical response in patients seen at various stages of the disease. Certain observations have been possible with regard to dosage, schedules, routes of administration and the concomitant use of sulfonamides.

Acute bacterial meningitides, produced by organisms other than the meningococcus, are always sporadic and usually occur secondarily to infection elsewhere in the body or following direct traumatic contamination. While sulfonamide therapy has been unusually successful in meningococcal meningitis and moderately so in streptococcal meningitis, it has been of limited value in the pneumococcal and staphylococcal varieties. Today, the reported death rates in meningococcal meningitis are often less than 5% and rarely exceed 10%.[5] The effectiveness of the sulfonamides in acute streptococcal infections and especially those in the rigid, pneumatic chambers of the head such as

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mastoiditis and sinusitis has resulted in a marked reduction in the incidence of streptococcal meningitis. Not only has the early use of sulfonamides in these localized infections prevented hazardous complications, but they have been effective in reducing the mortality in established streptococcal meningitis from more than 90% to less than 35%.[2]

With this decline in the incidence of streptococcal meningitis, the pneumococcal infection has become the greatest problem, from the standpoint of frequency, mortality, and relative resistance to sulfonamide treatment. Before the use of chemotherapy, only an occasional patient recovered from pneumococcal meningitis. Sulfonamide therapy has resulted in widely diverse experiences in these infections, probably because of the limited number of cases and their tremendous variation in severity and extent of involvement. Today, the overall mortality in this disease is probably in the neighborhood of 80%.[5]

Many reports in which sulfonamide therapy was used show a much lower death rate; however, the numerous isolated unreported fatal cases must be taken into consideration. This is supported by the report of Dowling *et al.*[3] who surveyed the results in Washington, D. C., from January 1, 1938, to December 31, 1941, and found that only 4 of 72 cases survived. All 72 of these patients received sulfonamide therapy and many were given specific serum in addition.

Staphylococcal meningitis is considerably more uncommon than any of the other meningitides caused by cocci. In spite of chemotherapy, the death rate in this disease has remained high, although occasional recoveries have been reported.

In view of the powerful action of penicillin against coccal infections, it was hoped that the results in meningitis caused by these organisms could be significantly improved. This report comprises the results obtained in 71 patients with acute meningitis who were treated with penicillin. These cases were distributed as follows: 50 pneumococcal, 12 meningococcal, 5 streptococcal, and 4 staphylococcal meningitis. We have attempted to evaluate the effectiveness of penicillin without the addition of other forms of therapy, although with few exceptions these patients had received sulfonamides prior to the use of penicillin and in 10 cases a combination of penicillin and sulfonamides was used.

This study was made possible by the coöperation of a large number of physicians in 18 hospitals in the Philadelphia area. Approximately 60% of the cases were treated in teaching institutions. The authors controlled the dosage in all cases and the routes and intervals of administration in most of them. We attempted to see the patients frequently or follow their course through communication with their attending physicians. The general management and supportive care was left to the discretion of the physician in attendance. We feel that this type of experience enhances the value of the results obtained, since it offers an indication as to what may be expected in purulent meningitis with the more general use of the drug; however, limitations of supply and the lack of prolonged experience with the drug probably altered the final outcome in many of the 71 cases.

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**Pneumococcic Meningitis.** In this series of 50 cases of pneumococcic meningitis treated with penicillin, the mortality was 64%. In comparison with more recent reports on sulfonamide therapy, this does not suggest that any very significant advance has been made. Rhoads *et al.*[12] reported 22 patients treated with sulfapyridine and specific serum with a mortality of 68%. Neal and her associates[8] presented 30 cases with 67% mortality. More recently Hodes, Smith and Ickes[6] reported 60 cases with a final mortality of only 58.3%. Waring and Smith[15] published a series of 12 cases treated with combined penicillin and sulfonamide therapy with only 1 death. The higher mortality in our series may have been significantly influenced by the large proportion of aged patients, several of whom died of secondary non-infectious complications, and the inadequacy of therapy in many of the first cases treated, both in respect to total daily dosage and the duration of treatment. Of the patients in this series, 7 were given combined penicillin and sulfonamide therapy, 4 of whom died, giving approximately the same ratio of fatalities as in the entire group.

One of the most striking features of pneumococcal meningitis is the diversity in form of its clinical course. This is particularly obvious when these cases are compared with the more uniform meningococcal meningitis. In our experience the most important variables which influence survival, other than those pertaining to specific therapy, are age and the source of infection. The patients in this series varied from 1 month to 72 years of age; 21 were less than 16 years of age, 12 of whom (57.1%) died. Further breakdown of these 21 cases does not reveal any significant difference between infants and older children. Of 12 patients, 31 to 50 years of age, only 5 (42%) succumbed to the disease. Of 17 patients over 50 years of age, only 2 recovered (Table 1).

TABLE 1.—PNEUMOCOCCIC MENINGITIS (SIGNIFICANCE OF AGE)

| Age group (yrs.) | Recovered | Died |
|---|---|---|
| Less than 2 | 5 | 7 |
| 2–5 | 2 | 1 |
| 6–15 | 2 | 4 |
| 16–30 | 0 | 0 |
| 31–50 | 7 | 5 |
| 51 and over | 2 | 15 |

Pneumococcal meningitis in 29 cases occurred secondarily to uncontrolled infection in the air-containing spaces of the head. In 23 instances the primary focus was found in the middle ear or mastoid, and in 6 in the paranasal sinuses. Of the patients, 9 developed meningitis subsequent to pneumonia, in only 5 of whom were the blood cultures positive. The primary focus was not determined in 12. The mortality in the 29 cases having foci in the head was 71.4% and 55.5% in the 9 cases occurring secondarily to pneumonia. In those with undetermined foci, 6 (50%) died. Many of these foci were not determined until necropsy was performed. The higher death rate in those having subcranial foci indicates the inadequacy of penicillin alone in effectively controlling these infections (Table 2).

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TABLE 2.—PNEUMOCOCCIC MENINGITIS (POSSIBLE PRIMARY FOCI OF INFECTION)

| | Recovered | Died | Total |
|---|---|---|---|
| Ears and mastoids | 7 | 16 | 23 |
| Paranasal sinuses | 1 | 5 | 6 |
| Pneumonia | 4 | 5 | 9 |
| Undetermined | 6 | 6 | 12 |
| Total | 18 | 32 | 50 |

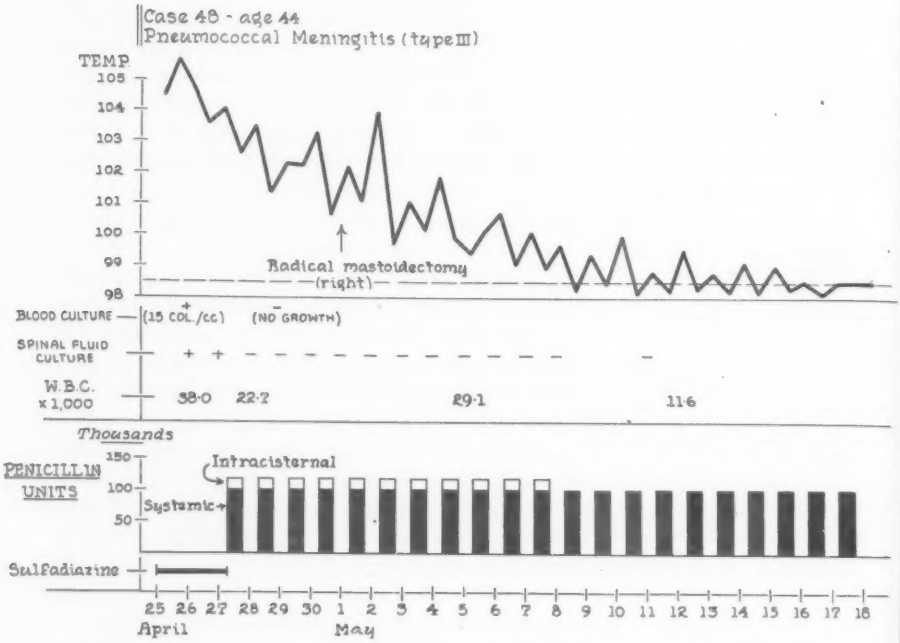


CHART 1.—Pneumococcal meningitis treated with systemic and intracisternal penicillin therapy. Radical mastoidectomy was performed which resulted in prompt improvement.

On several occasions it was noted that patients improved primarily with penicillin therapy and then entered a prolonged period of low grade sustained infection or repeated reinfection. In 5 patients the spinal fluid became clear and the temperature reached normal after 3 or 4 days of treatment, but then cloudy fluid and fever reappeared after a few days. Of the 5 patients, 2 ultimately recovered, while in 2 of the 3 fatal cases there was complete recrudescence of the disease in all of its original severity, even though the administration of systemic and intrathecal penicillin had been uninterrupted. All of these relapses appeared to be due to uncontrolled foci in the mastoid. Of the more recently treated patients with primary mastoid foci, 4 were subjected to radical mastoidectomy. Three of the 4 showed prompt improvement after operation and recovered (Chart 1).

Satisfactory pneumococcus typing was obtained in 46 of the 50 cases. Type III occurred with the greatest frequency and was recovered

from 7 of the meningitic infections, 4 of which resulted from otitic foci. This agrees with the findings of other investigators.[2,3] Types III, IV and V produced approximately one-third of the infections, while Types I through VIII were the responsible organisms in 26 of the 46 pneumococcus typed cases. The primary infection in 17 of the 26 was otitis media or mastoiditis. Meningitis secondary to pneumococcal pneumonia and sinusitis appeared to be more random in regard to specific types. There was no essential difference in mortality between the infections produced by the lower types and the higher types of pneumococci.

Blood cultures were done in 41 of the 50 cases, 23 of whom demonstrated bacteremias while 18 did not. The mortality was somewhat greater with bacteremia. Three bacteremic cases displayed acute vegetative endocarditis at autopsy. This complication was suspected in another fatal case upon whom necropsy was not performed (Table 3).

TABLE 3.—PNEUMOCOCCIC MENINGITIS (SIGNIFICANCE OF BACTEREMIA)

| | Recovered | Died | Total |
|---|---|---|---|
| With bacteremia | 8 | 15 | 23 |
| Without bacteremia | 8 | 10 | 18 |
| No blood culture | 2 | 7 | 9 |
| Total | 18 | 32 | 50 |

The systemic dosage of penicillin varied widely. During the early part of this study supplies of the drug were usually limited and occasionally treatment had to be discontinued because of exhaustion of supply. The later patients in the series were given 100,000 units per day to adults, adjusting the route of administration, intramuscular or continuous intravenous, to the acuteness and severity of the individual case. (There is a trend toward giving larger doses of penicillin in severe infections, now justified by the increasing availability of the drug, and in view of our relatively unsatisfactory results with the dosage we have employed, it would appear to be wise to give at least 200,000 units per day during the acute phase of the disease.) The smallest daily dose used in any of these cases was 25,000 units in infants, and 50,000 units in adults. The largest dose given was 180,000 units each day to an adult whose infection was extremely acute and severe. Among patients who recovered, the average total dosage was 1,400,000 units and the average duration of treatment was 15.5 days.

Nineteen patients received intramuscular therapy in equally divided doses every 2 or 3 hours, 12 of whom recovered with a resultant mortality of 37%. The remaining 31 cases received intravenous therapy, either throughout their course of treatment or until they improved sufficiently to justify a change in administration. Twenty-five (80.6%) of these patients died. These figures do not assign any significance to the route of administration since the more acutely ill patients received intravenous therapy.

*Intrathecal Therapy.* The work of Rammelkamp and Keefer[11] with normal subjects indicated that intravenously administered penicillin

did not readily cross the blood-brain barrier and that intrathecal therapy was necessary for the successful treatment of meningitis. Rosenberg and Sylvester[14] recently reported the recovery of effective concentrations of the drug in the spinal fluid of patients with meningitis following systemic administration of 20,000 to 40,000 units. Pilcher and Meacham,[9] studying the effect of penicillin on experimental staphylococcal brain lesions in dogs, found that the survival rate with intravenous penicillin was essentially the same as in the control cases, while intrathecal therapy resulted in a reduction in mortality from 93% in control animals to 54% in the experimental animals. All but 7 of the 50 cases in our series received intrathecal therapy. Three of the 7 recovered and 4 died. In 2 of the 3 recoveries response to systemic therapy was prompt, but the 3rd case became spastic and improved very slowly. Of the 4 who died, 2 were under treatment less than 24 hours and 2 demonstrated tremendously increased spinal fluid pressure. It would not be wise to rely upon local therapy alone in pneumococcal meningitis, since the primary foci of infection are seldom, if ever, in adequate contact with the spinal fluid. Pilcher and Meacham,[10] working with experimental pneumococcal meningitis in dogs, not only demonstrated the advantages of intrathecal therapy, but also showed that local therapy alone was not adequate.

The intrathecal administration of penicillin can be carried out by injecting the material intraspinally, intracisternally, and intraventricularly. The latter may be accomplished through the open anterior fontanelle of infants, while the use of this route in older children and adults, of course, necessitates making burr holes in the skull. Two infants, one 4 weeks of age and the other 4 months old, received intraventricular penicillin through the anterior fontanelle. The older patient recovered, the other died within 48 hours without evidence of trauma or reaction to the procedure. Intracisternal penicillin therapy was given to 15 patients without ill-effects, except in 2 instances in which the fluid was slightly bloody at the next tap. Both of these patients recovered from their meningitis, although 1 died subsequently from other causes. In this group of cases it is impossible to compare adequately the results obtained with intracisternal or intraventricular therapy and intraspinal therapy, since the routes of administration were frequently combined, or altered as the patient's condition changed. However, the mortality in 28 who received local therapy by the lumbar route alone was 75%, while in the group of 15 cases who received some penicillin at a higher site of injection it was only 46.7%. This appears to suggest superiority of the intracisternal and intraventricular administration over the intraspinal route. Rammelkamp and Keefer[11] reported that the drug was detectable in the spinal fluid within the skull after intraspinal administration, but in many patients with purulent meningitis there may be a partial mechanical block from plastic exudate. Four patients who had failed to improve with intraspinal therapy responded promptly to intracisternal administration. All 4 recovered.

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We have increased the range of intrathecal dosage since we treated the 1st case by this technic 1½ years ago. Of the 43 cases who were given this type of therapy, 21 received 10,000 units per day and one-third of them recovered. Of 14 who received smaller doses, 10 (71.4%) died. The administration of 15,000 to 20,000 units intrathecally each day to 8 patients resulted in a mortality of 50%. The drug was usually given intrathecally only once a day. Three acutely ill patients were injected twice daily. All 3 died. The smallest volume used for intrathecal injection was 3 cc. in infants and the largest 20 cc. in adults. The usual volume was 10 cc. per injection. Both physiologic salt solution and spinal fluid were used as diluents.

The only significant reaction observed as a consequence of the intrathecal use of penicillin is occasional pleocytosis of the spinal fluid. This reaction is becoming more infrequent as the processes of manufacture permit the production of a more refined penicillin. Four patients in this series developed pleocytosis and all of them died while the fluid was still cloudy; however, there was no evidence of blockage or increased intracranial pressure.

*Adequacy of Therapy.* If one considers only those cases who received at least 100,000 units in the first 24 hours, supplemented with 10,000 units intrathecally and did not die of other causes, it appears that the 26 cases so qualified showed a mortality of 42.3%.

In our results there is no significant correlation between the onset of the disease and the date when penicillin treatment was instituted. Twenty cases treated within the first 44 hours of the disease showed a mortality of 70%, while 18 treated after 6 or more days showed essentially the same death ratio. Those treated between the 3rd and 5th day of the disease showed recovery of 7 out of 12 cases. This difference probably is not significant because of the small series; however, the results may have been influenced by the highly lethal fulminating cases on the one hand, and the more established lesions in those with older infections on the other.

All but 3 patients in this series had received sulfonamide therapy prior to the administration of penicillin. Sulfonamide treatment was usually discontinued when penicillin was started, although in 7 cases a combination of penicillin and sulfonamide therapy was administered when the former drug alone appeared inadequate. Three of these recovered. Specific antipneumococcic serum was used in conjunction with sulfonamide therapy and penicillin in 3 of the 47 cases, and only 1 recovered.

*Reactions.* The administration of penicillin did not appear to be harmful in 45 of the patients. As mentioned above, pleocytosis occurred in 4 individuals, while 1 patient developed a generalized urticaria. All 5 of these patients died. Whether or not these reactions played any significant part in contributing to death could not be determined. In a 9-months-old infant who displayed a pneumococcus Type XIV meningitis which arose from bilateral mastoiditis, the course of systemic and intrathecal therapy was prolonged and given in adequate concentrations by suitable techniques. This child showed

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an oscillating response, for at times he seemed to improve, only to show cloudy fluid again after a few days. Every effort was made to control this infection over a period of 32 days, including the addition of sulfonamide therapy and the administration of specific sera intravenously and intrathecally. Penicillin was administered twice daily intraspinally for 8 days. While there was never any evidence of penicillin reaction, about a week before death *B. coli* appeared in the spinal fluid. In spite of renewed efforts, the patient died and at autopsy the pneumococcus Type XIV and *B. coli* were cultured from the meninges. It was at necropsy that the bilateral mastoiditis was finally established. While this case does not illustrate a drug reaction, in fact, the child seemed to improve on penicillin, it does adequately emphasize the possibilities of contamination and the need for strictest asepsis in subarachnoid punctures.

Two patients, 1 of whom recovered, showed evidence of marked crystalluria, hematuria, and possible ureteral blockage from sulfonamide administration prior to the use of penicillin. Another patient receiving combined therapy developed a skin rash and a bilateral conjunctivitis, both of which quickly disappeared after the sulfonamide was discontinued. Penicillin was not stopped until the patient had recovered.

The development of localized or generalized spasticity and psychosis was a common occurrence in this series of cases. Four children became spastic, 3 of whom survived. In all 3 the spasticity improved slowly after the infection was controlled. One of these patients who recovered did not receive any intrathecal therapy. There were 4 patients who showed mental disturbances, only 1 of whom recovered from the infection. This patient was transferred to a mental institution soon after penicillin was discontinued where she remained for $3\frac{1}{2}$ months before she died.

*Deaths.* Of the 32 deaths in this series, 12 occurred in the first 48 hours after penicillin treatment was started. The remaining 20 cases, after 2 days of therapy, showed varying degrees of response prior to death. Some of them improved only slightly, while others were apparently cured of meningeal infection and succumbed to other complications.

Necropsies were performed on 20 of the 32 fatal cases. The cause of death in 10 of the 20 was thought to be an overwhelming meningitis. The extent of involvement in these cases varied from a localized basilar meningitis to panmeningeal involvement. In 4 cases secondary brain abscesses were thought to be the principal cause of death. Positive blood cultures had been obtained in only 1 of the 4. The rupture of a lung abscess resulted in death of a 7-year-old boy, in whom the meningitis was improving on penicillin therapy. Another patient, a 66-year-old woman, died with a lung abscess and considerable cerebral deterioration several weeks after meningitis had been controlled. Three cases were found to have acute vegetative pneumococcal endocarditis at autopsy. The remaining patient had apparently recovered from his meningitis and was being treated for a concomitant

putrid empyema which ruptured into the bronchus and resulted in suffocation.

**Meningococcal Meningitis.** Meads, Harris, Samper and Finland[7] recently reported 9 cases of meningococcal meningitis treated with intrathecal and systemic penicillin. They studied these patients exhaustively and concluded that the response to penicillin in meningococcal meningitis is somewhat slower than to the sulfonamides. They also found that several strains of meningococci recovered from these patients were relatively resistant to penicillin. Rosenberg and Arling[13] reported 71 cases treated with penicillin with only 1 fatality; however, it is not known whether sulfonamides were incorporated in the treatment or not.

Our results in 12 cases, in which there were 6 deaths, are not indicative of the effectiveness of penicillin, but serve to illustrate the limitations of this drug in controlling the more severe and resistant meningococcal infections (Table 4). Seven of the 12 patients were given penicillin after adequate sulfonamide therapy had failed. In 2 of the 7 there was no bacteriologic evidence of infection when penicillin was started. Four of these 7 patients died.

TABLE 4.—MENINGOCOCCAL MENINGITIS

| No. | Age | Sex | Bacteremia | Daily penicillin dosage | | Results |
|---|---|---|---|---|---|---|
| | | | | Systemic | Local | |
| 1 | 27 | M | No | 100,000 | None | Rec. |
| 2 | 25 | F | Yes | 100,000 | None | Rec. |
| 3 | 63 | M | No | 100,000 | 10,000 | Died |
| 4 | 5 | M | (No cult.) | 50,000 | None | Rec. |
| 5 | 31 | F | Yes | 100,000 | None | Died* |
| 6 | 37 | M | No | 100,000 | None | Rec. |
| 7 | 2 | F | Yes | 50,000 | None | Died |
| 8 | 21 | M | No | 100,000 | None | Died |
| 9 | 2 | M | No | 100,000 | 16,800 | Died |
| 10 | 15 | F | Yes | 100,000 | 10,000 | Rec.* |
| 11 | 1 | F | Yes | 100,000 | 62,000 | Rec. |
| 12 | 47 | F | No | 100,000 | 10,000 | Died |

* Waterhouse-Friderichsen syndrome.

The remaining 5 cases included 2 who had received less than 8 hours of sulfonamide therapy and 3 who were given penicillin as the primary and only form of therapy. Two of the 5 patients were *in extremis* and died within 24 hours after penicillin was started. One of them had been given 2 doses of sulfadiazine.

Penicillin and sulfonamides were combined in 2 patients, both of whom recovered.

The systemic dosage used was 100,000 units daily except for 2 children, both of whom received 50,000 units each day. The drug was given by continuous intravenous drip during the acute phase in 9 cases and by intramuscular injection in 3, all children. Among those who recovered, the average total dose was 750,000 units during an average of 6.5 days of treatment.

The 2 fatal cases who were *in extremis* when penicillin was started had an inadequate period of therapy in respect to duration and total

dosage. The 4 remaining cases which terminated fatally received ample therapy.

Only 5 of the 12 patients were given intrathecal therapy. Three of the 5 died. The intraspinal route was used in 3; the intracisternal method in 2. The daily intrathecal dosage in 3 patients was 10,000 units, 16,800 units in another, and the remaining patient received 20,000, 41,000, 63,000 and 50,000 units at various times. There was no evidence of reaction to intrathecal administration in any of the 5.

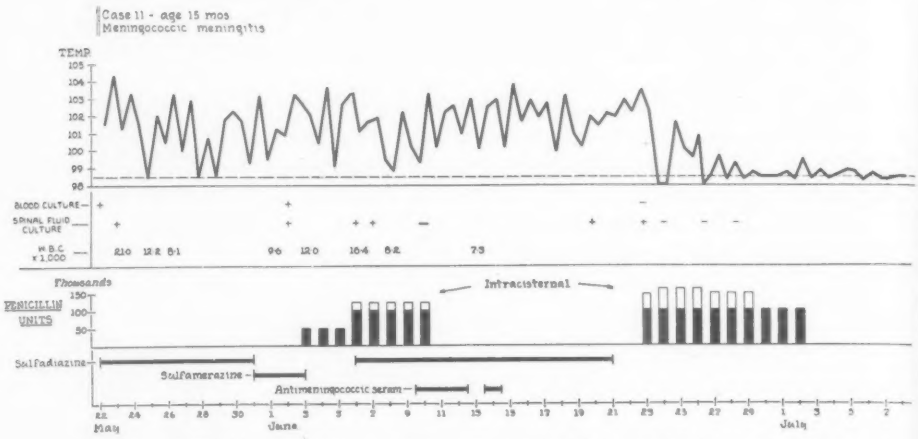


CHART 2.—Highly resistant meningococcal meningitis treated with massive intracisternal penicillin therapy (as high as 62,000 units daily) resulting in prompt response.

**Case Abstract.** The patient who received the massive intracisternal therapy (Chart 2) was a 15-month-old white female. She was admitted to the hospital on May 22, 1944, with acute meningococcemia and meningitis. Sulfonamide therapy was given in large doses until June 3, 1944, without significantly altering the course of the disease. The bacteria remained present both in the spinal fluid and blood. Sulfonamide was discontinued on June 3, 1944, and a course of penicillin therapy begun. She received 50,000 units daily by intramuscular injection without appreciable effect. On June 6, 1944, the systemic dosage was increased to 100,000 units daily. In addition, 20,000 units were given intracisternally and sulfadiazine was again added to the treatment. By June 10, 1944, there was still no therapeutic response and penicillin was discontinued. A combination of massive sulfonamide therapy and intermittent specific serum injections were continued until June 21, 1944. All forms of therapy were then stopped for 54 hours, during which time the temperature rose slightly and the child became much more toxic. On June 23, 1944, the blood culture was sterile, but the spinal fluid still contained viable meningococci. On this date systemic penicillin therapy of approximately 100,000 units each day was started again. Sulfonamides were not given. Along with the systemic penicillin, the following doses were given intracisternally: June 23, 41,000 units; June 24, 62,000 units; June 25, 62,000 units; June 26, 62,000 units; and 50,000 units June 27, 28 and 29. With this massive therapy the child began to improve promptly, the spinal fluid became sterile and began to clear and by June 28 the temperature approached the normal range and did not exceed 99.6° F. thereafter. She was discharged from the hospital July 11, 1944, completely cured.

Seven patients received no intrathecal therapy, 3 of whom were given no sulfonamide medication. There were 3 deaths among the

7 cases, 1 occurring in a patient who received only penicillin. The recovery of 4 patients with systemic therapy alone, all of whom had positive spinal fluid cultures when penicillin was started, suggested that systemically administered penicillin does cross the blood-brain barrier in sufficient concentration to be effective in some cases.

Among the 6 patients who recovered, 3 responded promptly in a manner similar to the usual sulfonamide effect (Chart 3). The remaining 3 showed varying degrees of delay in response. All 3 had received sulfonamide therapy previously and it was combined with penicillin in 2 of the 3 cases. This experience does not indicate any significant lag in response to penicillin as compared with the sulfonamides.

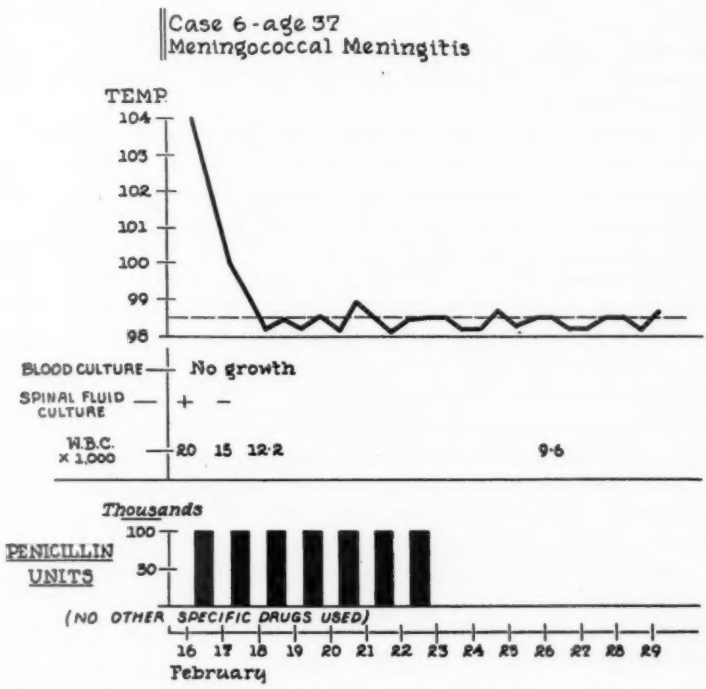


CHART 3.—Meningococcal meningitis showing prompt response to systemic penicillin therapy alone.

Two of the 12 patients demonstrated findings suggestive of a Waterhouse-Friderichsen syndrome. One patient who died 12 hours after the onset of the disease was found to have a hemorrhagic right adrenal at necropsy. She had meningococcemia as well as meningitis. The other patient, a girl of 15, had an acute onset associated with nausea, vomiting and abdominal pain and distention. A rash appeared approximately 12 hours later and the patient was semicomatose and in shock soon thereafter. The rash which at first was petechial and distributed chiefly to the extremities and face, soon became dark and blotchy. At the time of admission the temperature was over 107° F.

The blood pressure was consistently low for 5 days after admission to the hospital and the blotchy purpuric areas progressed to gangrene and sloughing which greatly delayed her final recovery. Penicillin was started soon after admission and was given intrathecally as well as intravenously. Two days after admission sulfadiazine was added to the therapy, since she had remained unconscious and febrile. She responded very slowly but with progressive gradual improvement.

**Streptococcal Meningitis.** Our experience with penicillin therapy in acute streptococcal meningitis has not been significant because of the limited number of cases and their extreme complexity. These results are included merely for the sake of completeness and to demonstrate the limitations of penicillin therapy, even in infections caused by highly susceptible organisms, when there is a preponderance of circumstances which limit or prevent the possibilities of recovery. Only patients who had failed to respond to sulfonamide treatment were given penicillin.

Five patients with streptococcal meningitis were treated with penicillin and only 1 of the 5 recovered (Table 5). Three of the 4 fatalities occurred in patients who were moribund at the onset of penicillin therapy, 2 of whom died within 36 hours. The single recovery occurred in an infant 3 months of age in whom meningitis developed secondary to a bilateral otitis media. Penicillin was started soon after admission before the child had received any other form of therapy. For 2 days she received 100,000 units daily by equal 2-hourly intramuscular injections. Thereafter for 4 days she was given 50,000 units each day by the same route. Ten thousand units were given intracisternally each day in conjunction with the systemic therapy. Systemic sulfadiazine was started on the 4th day of penicillin treatment since the fluid was still cloudy, although sterile culture was obtained; the temperature had remained elevated and nuchal rigidity was still present. Sulfadiazine was continued for 12 days after penicillin had been discontinued. Bilateral myringotomy was done soon after admission. In this case it is impossible to determine the respective rôles which penicillin, sulfadiazine and myringotomy played in contributing to recovery.

TABLE 5.—STREPTOCOCCAL MENINGITIS

| No. | Age | Sex | Bacteremia | Daily penicillin dosage | | Results |
|---|---|---|---|---|---|---|
| | | | | Systemic | Local | |
| 1 | 10 | M | No | 80,000 | 10,000 | Died |
| 2 | 76 | M | Yes | 100,000 | 10,000 | Died |
| 3 | 52 | M | Yes | 150,000 | 10,000 | Died |
| 4 | 60 | F | No | 90,000 | 10,000 | Died |
| 5 | 3/12 | F | (No cult.) | 100,000 | 10,000 | Rec. |

Among the 4 patients who died, 1 was 10 years of age, while the others were 52, 60 and 76 years old respectively. All 4 had received an ample course of sulfonamides prior to the use of penicillin. The drugs were not given together in any of the 5. All 4 received adequate intravenous and intrathecal penicillin therapy. There were no sulfonamide or penicillin reactions of any kind. One of the 4 received

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3 intraventricular instillations of the drug before she died, 36 hours after penicillin was started. In 3 of the 4 the spinal fluid had become sterile before penicillin was started. In the remaining case only 1 fluid specimen was obtained, since the patient died within 24 hours.

The primary foci of infection among the fatal cases were found to be: otitis media, cellulitis of the eye with osteomyelitis of the orbit, an infected cerebellar scar (which was incised), and a diabetic foot infection which resulted in bacteremia and endocarditis as well as meningitis.

The organism in 4 of the 5 cases was beta-hemolytic streptococcus, while the spinal fluid of the 5th patient revealed anaerobic non-hemolytic streptococci. The cause of death in 2 cases was listed as purulent basilar meningitis, as subdural abscess in another, and as acute endocarditis in the remaining case.

**Staphylococcal Meningitis.** The results obtained with sulfonamide therapy in staphylococcal meningitis have been less satisfactory than those obtained with sulfonamides in other forms of acute coccal meningitis. This disease is the more infrequent of the secondary meningitides and has always been considered to be more lethal.

The great specificity and potency of penicillin against hemolytic *Staphylococcus aureus* infections is well illustrated in the 4 patients included in this series (Table 6). All 4 of them recovered from their acute infection, although 1 of them died 3½ months after the infection had been controlled and apparently eliminated by the use of penicillin. This patient was a 22-year-old female, admitted because of sensory disturbances in the lower extremities. A staphylococcal bacteremia and meningitis developed subsequently which was treated successfully with penicillin. During her course of acute infection and therapy she displayed localizing signs. A laminectomy was done between $D_4$ and $D_6$ which revealed a subdural abscess and cord compression. The infection had apparently extended into the vertebra. Subsequently the patient developed a cord bladder, loss of sensory and motor power in the left lower extremity, and large decubiti over the bony prominences in the involved areas. She lived almost 4 months after the laminectomy. A septic abortion 3 months before admission may have been the original portal of entry.

TABLE 6.—STAPHYLOCOCCAL MENINGITIS

| No. | Age | Focus | Bacteremia | Daily penicillin dosage | | Result |
|---|---|---|---|---|---|---|
| | | | | Systemic | Local | |
| 1 | 33 | L2 | No | 100,000 | None | Rec. |
| 2 | 3 | Craniotomy | (No cult.) | 50,000 | 10,000 | Rec. |
| 3 | 22 | Uterus? | Yes | 100,000 | 10,000 | Rec.* |
| 4 | 3 | Craniotomy | No | 25,000 | 10,000 | Rec. |

* Died 2½ months after meningitis was cured.

The other 3 patients included 2 3-year-old children who developed meningitis as a postoperative complication following removal of cerebellar tumors. The remaining case (Chart 4) was an adult who displayed chronic recurrent osteomyelitis which, at this admission,

involved the second lumbar vertebra. He displayed left ear deafness, left arm paralysis, and acute staphylococcal sinusitis during the acute infection. None of these last 3 patients showed staphylococcemia.

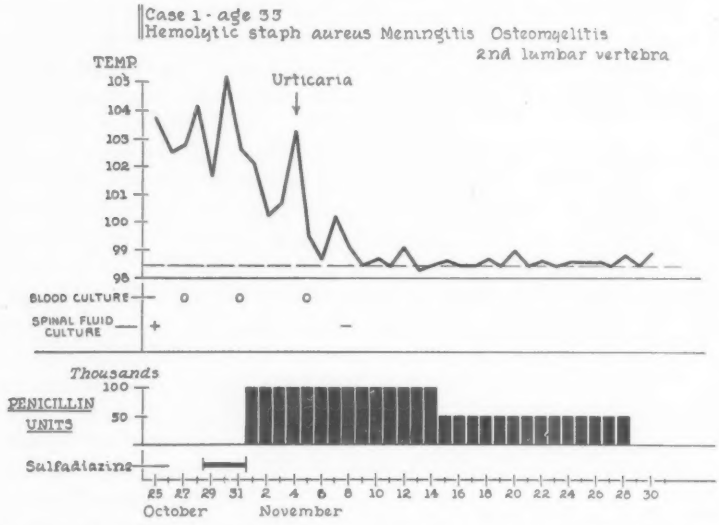


CHART 4.—Hemolytic staphylococcus meningitis treated with systemic penicillin therapy alone.

The 2 adult patients were given 100,000 units of penicillin each day, first by the continuous intravenous route and later by intermittent intramuscular injection. The 2 children received 25,000 units and 50,000 units, respectively, each day by intramuscular administration.

Intrathecal therapy in the 2 children was given intraventricularly through the operative cranial defect. The patient with the subdural abscess was given intracisternal therapy. The remaining patient who had osteomyelitis of the second lumbar vertebra did not receive any intrathecal therapy (Chart 4). His response was prompt and adequate to the systemic therapy. He displayed an urticarial rash 4 days after penicillin was started.

These patients had all received sulfonamides before the institution of penicillin treatment, but progress was not considered to be satisfactory. The evidence of meningitis in all 4 cases consisted of purulent spinal fluid containing viable organisms withdrawn on at least 2 occasions before penicillin was begun. The hemolytic *Staphylococcus aureus* was recovered in all 4.

**Discussion.** Despite the limitations of penicillin in purulent coccal meningitides, it appears that this drug will find a place in the therapy of these diseases unless it is supplanted by a more efficacious drug. While future study may reveal that the sulfonamides are equally or more effective in meningococcal and streptococcal meningitis, penicillin should be employed in those cases which do not respond after adequate trial of sulfonamides. It seems probable that penicillin will be the

primary drug of choice in the pneumococcal and staphylococcal meningitis.

There are now 2 major questions which confront us regarding the use of penicillin in meningitis. First, should it be given in combination with sulfonamides? And second, is intrathecal therapy necessary? In view of our experience and the reports which have appeared in the literature on this subject,[7,9,10,13,14] we believe that both questions should be answered in the affirmative.

Since penicillin and sulfonamides have been shown to be of definite value in types of meningitis discussed in this paper, and since they are, as far as we know, completely compatible, there is no rational reason for not combining them. When the 2 drugs are used simultaneously the combined result may be due to synergistic action,[1] or merely to the cumulative effect. Although combining of therapeutic agents may be unsatisfactory from the standpoint of clinical research, suppurative meningitis is an exceedingly serious type of infection and the combined use of all available measures of possible therapeutic value would appear to be justified in routine practice (Table 7).

TABLE 7.—COMBINED PENICILLIN AND SULFONAMIDE THERAPY

| Meningitis | Recovered | Died | Total |
|---|---|---|---|
| Pneumococcal | 3 | 4 | 7 |
| Meningococcal | 2 | 0 | 2 |
| Streptococcal | 1 | 0 | 1 |
| Staphylococcal | 0 | 0 | 0 |
| Total | 6 | 4 | 10 |

The question of intrathecal therapy is far from settled. In this report we have mentioned 15 patients treated with penicillin alone who did not receive intrathecal injections. Eight of these patients recovered, apparently as a result of this therapy. These cases are distributed as follows: 7 pneumococcal infections with 4 deaths, 7 meningococcal with 3 deaths, and 1 staphylococcal, who survived. This indicates that intrathecal treatment is not always indispensable, but while doubt remains, we are disposed toward the opinion that the severity of these infections calls for complete therapeusis by all rational methods (Table 8). Furthermore, penicillin injected by ventricular and cisternal routes is likely to be more effective than that given into the lumbar canal.

TABLE 8.—PATIENTS RECEIVING ONLY SYSTEMIC PENICILLIN THERAPY

| Meningitis | Recovered | Died | Total |
|---|---|---|---|
| Pneumococcal | 3 | 4 | 7 |
| Meningococcal | 4 | 3 | 7 |
| Streptococcal | 0 | 0 | 0 |
| Staphylococcal | 1 | 0 | 1 |
| Total | 8 | 7 | 15 |

The results presented in this report indicate that results with penicillin in pneumococcal meningitis are not significantly better than those obtained with sulfonamides in the hands of experienced clinicians. However, improved results with penicillin are to be expected as clinical experience increases and as cases are treated earlier in their course. The statistical results in this study were heavily weighted

by the inclusion of many patients who had already failed to respond to sulfonamide treatment. If more of the patients had received penicillin early, rather than as a measure of desperation, a larger proportion of survivals might have been recorded.

Virtually the same comments apply in connection with meningococcal meningitis.

The streptococcal meningitis patients in this series were at such advanced states of illness that there remained no reasonable expectation of successful treatment.

Penicillin appears most highly specific for the staphylococcal infections and should be used promptly as the drug of choice in all cases of meningitis caused by this organism.

Since the great majority of cases of streptococcal, pneumococcal and staphylococcal meningitis are secondary to infection elsewhere in the body, an intensive search for every possible focus is imperative.[4] Every patient should be examined by a competent otolaryngologist, and complete Roentgen ray studies of mastoids and paranasal sinuses should be performed with due recognition of the frequency with which the signs of infection in these areas are masked by chemotherapy. The urgency of this step is based on the likelihood that the drug therapy will not influence a primary suppurative focus and that constant refeeding of blood stream and meninges from such a focus will militate strongly against recovery. The slightest evidence of undrained abscesses in mastoids or sinuses demands early surgical intervention, even though such findings would not call for surgery in the absence of meningitis. Operative procedures are relatively safe in a patient protected against generalization of infection by penicillin.

Our random experience in the treatment of 71 cases of acute meningitis with penicillin during the period of preliminary clinical evaluation of the drug does not justify specifications of the ideal regimen of therapy in the management of these infections, particularly when the factors of increasing supply and decreasing costs of penicillin are taken into consideration. However, it appears that the following comprises a safe and useful plan of therapy until more extensive investigation establishes an optimal course of treatment:

1. Prompt diagnosis and ample supportive therapy, including surgical intervention if indicated.

2. Two hundred thousand units of penicillin administered systemically each day by the continuous intravenous route during the acute phase of the disease and later by intermittent intramuscular injection as the infection is brought under control.

3. Ten thousand to 20,000 units of penicillin intracisternally once or twice each day.

4. Ample sulfadiazine or sulfamerazine therapy systemically to attain blood levels of over 15 mg. % of free drug in conjunction with the administration of penicillin.

5. Continuation of intracisternal penicillin until 4 days after the spinal fluid has cleared and nuchal rigidity has begun to decrease, and of systemic penicillin therapy until 7 to 10 days after the disappearance of all signs of infection.

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**Summary.** Seventy-one cases of acute coccal meningitis treated with penicillin are presented. The following conclusions seem justified:

1. Penicillin was often effective in pneumococcal, meningococcal and streptococcal meningitis after adequate sulfonamide therapy had failed to produce the desired response.

2. In pneumococcal meningitis the presence of subcranial foci and advanced age were cardinal factors in influencing the mortality rate.

3. Intrathecal penicillin therapy does not appear harmful. Intracisternal injection seems to be the most effective route of intrathecal administration.

4. Although penicillin administered by the systemic route alone may have a curative effect in selected cases, it seems preferable to supplement systemic administration with intrathecal injections of the drug by the cisternal route.

5. The superiority of penicillin over other forms of chemotherapy is most clearly demonstrated in staphylococcic meningitis.

6. It is not unlikely that best results will be obtained through the use of a combination of penicillin and sulfonamides in systemic therapy, and penicillin intrathecally.

7. A plan of management of purulent meningitis based upon the authors' experience, is outlined.

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# INFECTIVE HEPATITIS

## With Special Reference to Prognosis

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The epidemic prevalence of acute infective hepatitis in the past 4 years has provided evidence for prognosis. The same disease in its sporadic form (hitherto known as catarrhal jaundice) was almost always benign, but it was known that in very occasional cases the clinical picture for unknown reasons might suddenly change and fatal hepatic failure ensue. We know nothing of the frequency of this happening, since most of the cases occurred in general practice and were probably seldom published.

During the present epidemic of the disease the prognosis is obviously benign in most cases, although recovery may be delayed for 3 months. On the other hand, there is evidence that the disease may occasionally pursue a different course, and end in: (1) acute fatal necrosis; (2) subacute damage, going on to: (*a*) gradual hepatic failure, (*b*) cirrhosis.

A marked rise in the incidence of acute hepatic necrosis was noted by Bergstrand[1] during the Swedish epidemic of jaundice in 1927. In the present epidemic of infective hepatitis in England, Ford[8] reported 1 death from acute necrosis in 300 cases, and Lisney[15] considered 3 or possibly 5 individuals died of the disease out of 1062 attacked. (It is however, probable that all of these deaths were not due to *acute* necrosis.) Under exceptionally favorable circumstances, at the U. S. Army Institute of Pathology, Lucke[15a] was able to study 125 fatal cases occurring in an unspecified (for obvious reasons) number of cases. However, he states that "only a small fraction of the cases" end fatally. Lucke does not state how many of the deaths were due to the spontaneous disease and how many occurred after the use of yellow fever vaccine. On the other hand, Edwards[6] had no deaths in 64 cases and Evans[7] none in 65 and there were no fatalities in 170 cases reported by Cameron[2] in the Palestine Forces and none in 168 cases reported by Gordon[9] in the Middle East Forces. As fatal cases, in the Services at least, are likely to come under observation in hospitals, it seems that acute necrosis is an infrequent termination of infective hepatitis at the present time.

There is a growing amount of evidence that the liver may sustain permanent, but not immediately fatal, damage from an attack of acute infective hepatitis. Bergstrand[1] and Cullinan[3,4] described a condition of subacute necrosis of the liver characterized by prodromal symptoms like those of acute infective hepatitis, by fluctuating jaundice and by enlargement of the liver and spleen. Many of the patients died of hepatic failure after a period of months or even years; in others ascites

and a tendency to hematemesis developed; apparent recovery was noted in some, but relapse was usual. At autopsy, subacute necrosis of the liver was found. More recently, Higgins, O'Brien, Stewart and Witts[12] classified as subacute all cases of hepatitis in which jaundice lasted longer than 2 months and reported 7 out of 19 to be probably due to acute infective hepatitis. Of these patients, 3 died (subacute necrosis of the liver being found at autopsy), 3 recovered and 1 showed progressive hepatic disease when last seen. In 14 of Lucké's[15b] cases where death occurred from unrelated causes, after recovery from infective hepatitis, all the livers appeared normal grossly. In all 9 cases examined more than a month after recovery, the "parenchyma was restored completely."

The development of cirrhosis after a variable period free from symptoms was also described by Bergstrand.[1] Polack[16] reported 8 cases in young adults after an attack of acute hepatitis 3 to 8 years before. In a review of 386 cases of cirrhosis, Ratnoff and Patek[19] concluded that catarrhal jaundice was the probable cause in 6.5%. Rennie[21] observed that in 5 out of 16 patients with cirrhosis, the only known antecedent factor was an attack of "catarrhal jaundice." Some attempts have been made to detect residual hepatic damage by performing function tests on individuals who have made an apparently complete recovery from acute infective hepatitis. Soffer and Paulson[22] and Kornberg[14] found a plasma bilirubin above the accepted normal level and a diminished bilirubin clearance in reëxaminations some years after the attack.

None of those patients with positive findings showed clinical evidence of hepatic disease although some complained of dyspepsia. More recently it has been reported that hippuric acid synthesis (Rennie;[21] Gordon[9]) and levulose tolerance (Rennie[21]) occasionally remain impaired some weeks after jaundice has disappeared. These results are inconclusive but suggest that the more modern tests of liver efficiency may reveal latent residual damage before clinical signs of cirrhosis develop.

This paper briefly summarizes the clinical manifestations shown by 39 patients in the acute stage of infective hepatitis. Six cases of subacute hepatitis and cirrhosis considered to be sequels to acute infective hepatitis are discussed in more detail. Liver efficiency tests were carried out on all patients and in many of them on numerous occasions.

In order to acquire more information about the ultimate issue of the disease it was also intended that observations should be continued after the patients were dismissed from the hospital, but present circumstances made this generally impracticable.

**Tests Used.** Hippuric acid synthesis (Quick[18]) as modified by Rennie,[20] a modified levulose tolerance test (Rennie[21]), estimation of plasma albumin and globulin (Howe[13] as modified by Hawk and Bergeim[10]) and the quantitative estimation of plasma bilirubin by the method of Thannhauser and Anderson[23] using the Lovibond comparator.

**Results in Controls.** *Hippuric Acid Synthesis.* The test was performed on 108 convalescent patients who were free of hepatic disease and were not suffering from any of the other conditions which diminish

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the output of hippuric acid. All tests were done with the subjects in bed. Over a period of 4 hours after ingestion of 6 gm. of sodium benzoate, the mean excretion of benzoic acid (as hippuric acid) in the urine was 3.18 gm. The range was 2.40 to 4.51, S.D. 1.06 and S.E. 0.10 gm.

*The Modified Levulose Tolerance Test.* Reasons for regarding the levulose tolerance test as specific have been given elsewhere (Herbert[11]) and a really high blood glucose such as may occur in diabetes would appear to produce the only fallacy. The plasma levulose was estimated ½ and 1 hour after ingestion of 50 gm. of levulose and the higher figure considered to be the significant one. In 30 controls drawn from the staff and patients convalescent from disease not involving the liver the maximum value was 14 mg. per 100 ml. The mean was 10.33, S.D., 1.14 and S.E. 0.21 mg. The extreme upper limit of normal has been taken as 15 mg. per 100 ml.

*The Plasma Proteins.* Estimation of the plasma albumin and globulin as a test of liver efficiency is based on the view that the liver is responsible for their synthesis. A number of workers have reported that albumin falls and globulin increases in various diseases of the liver, and very marked changes have been noted in cirrhosis (Post and Patek[17]) and in subacute hepatitis (Higgins, O'Brien, Stewart and Witts[12]).

As controls, 50 blood donors were used, the samples being taken at the start of the bleeding and with minimal stasis. The results are given in Table 1.

TABLE 1.—PLASMA PROTEIN VALUES IN 50 CONTROLS

| | (Gm. per 100 ml. of plasma) | |
|---|---|---|
| | Albumin | Globulin |
| Range | 4.19–5.78 | 1.48–3.09 |
| Mean | 4.91 | 2.33 |
| S.D. | 0.37 | 0.96 |
| S.E. | 0.05 | 0.07 |

*The Plasma Bilirubin.* The 50 blood donors also provided a series of observations on the bilirubin level in controls (Table 2).

TABLE 2.—PLASMA BILIRUBIN VALUES IN 50 CONTROLS

| Plasma bilirubin mg. per 100 ml. | No. of cases |
|---|---|
| None detected | 28 |
| 0.0–0.2 | 8 |
| 0.2–0.4 | 12 |
| 0.4–0.6 | 2 |

INFECTIVE HEPATITIS—ACUTE STAGE. *Clinical Manifestations.* Out of 39 patients, 37 gave a history of symptoms, predominantly gastrointestinal, before the appearance of jaundice, marked loss of appetite being a universal complaint. The duration of this pre-icteric stage varied greatly, being less than 1 week in 24 and more than 2 weeks in 3 instances. It is, however, probable that some patients failed to detect the jaundice at its onset. Two were confident that jaundice was the first sign of illness. Three patients stated that the urine

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was dark on the first day of illness and 1 of these, a doctor, detected bile in his urine 3 days before the development of icterus. Neither duration nor severity of the pre-icteric phase was related to depth or duration of jaundice.

The frequency of the symptoms and signs found in the hospital is shown in Table 3:

TABLE 3.—FREQUENCY OF SIGNS AND SYMPTOMS IN 39 PATIENTS WITH ACUTE INFECTIVE HEPATITIS

| | | | |
|---|---|---|---|
| Jaundice | 39 | Headache | 9 |
| Bile in urine | 39 | Joint pains | 8 |
| Marked anorexia | 39 | Albuminuria | 7 |
| Nausea | 30 | Pain in back | 3 |
| Vomiting | 25 | Spleen palpable | 2 |
| Abdominal pain or discomfort | 25 | Rash | 2 |
| Liver enlarged | 23 | Hemorrhagic tendency | 2 |
| Liver tender | 18 | Ascites | 2 |
| Pulse rate <60 p.m. | 21 | Edema | 1 |
| Fever | 13 | Herpes | 1 |
| Pruritus | 9 | | |

Leukocyte counts were made on 25 patients. The range was 2600 to 11,000 per c.mm. Nine patients had counts of less than 5000 per c.mm. Absolute lymphocytosis was found in 5 out of 10 differential counts. Extravasation of blood after venipuncture was prominent in 2 patients with deep jaundice associated with a low prothrombin index.

CASE 2 (Table 4) is of particular interest. This patient, a man of 42, underwent laparotomy because of intense and persistent jaundice associated with a mass thought to be the gall bladder. This mass was found to be a Riedel's lobe and his gall bladder, ducts and pancreas were normal. The liver was enlarged, very hard and dark green in color. Hepatic biopsy showed a picture which could be interpreted as a stage toward recovery from severe acute hepatitis. It was of interest that although the diffuse inflammatory infiltrate had gone, there was well-marked proliferation of the bile ducts. Cirrhosis was not present. Within a few weeks jaundice disappeared and the man was dismissed well. Two years later there was no sign of hepatic disease and liver efficiency tests were normal.

This clinical and biochemical recovery from a severe lesion is in accordance with the extraordinary and rapid restoration of hepatic structure noted by Dible, McMichael and Sherlock.[5]

At the time of dismissal from the hospital all the patients were subjectively and objectively well save for slight or minimal jaundice which was still present in the majority. The duration of the illness varied greatly and it was not possible to assess it from any of the initial clinical manifestations save one, jaundice. If jaundice was slight it did not last long. The converse did not necessarily hold good however, as deep jaundice sometimes lasted many weeks and, on the other hand, sometimes cleared rapidly.

*Biochemical Studies.* The results of tests on 39 patients with acute infective hepatitis are given in detail in Table 4. Initial observations showed that hippuric acid synthesis and levulose tolerance were impaired in 27 cases. Plasma albumin was reduced in 27, and globulin increased in 18 out of 34 cases.

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TABLE 4.—HEPATIC EFFICIENCY TESTS IN 39 CASES OF ACUTE INFECTIVE HEPATITIS

| Case No. | Date | Per 100 cc. of plasma | | | | Urine benzoic ā (gm. in 4 hrs.) | Duration of jaundice (wks.) on admission |
|---|---|---|---|---|---|---|---|
| | | Bilirubin (mg.) | Levulose (mg.) | Alb. (gm.) | Glob. (gm.) | | |
| 1 . . . | 10/ 3/41 | 16.2 | 22.2 | 3.83 | 2.57 | 0.86 | 1 |
| | 10/17/41 | 3.0 | 18.2 | 3.55 | 2.75 | 1.75 | |
| | 10/25/41 | 1.6 | 13.8 | 4.19 | 3.89 | 2.62 | |
| 2 . . . | 10/ 7/41 | 20.0 | 45.4 | 3.44 | 2.72 | 1.06 | 5 |
| | 10/25/41 | 3.0 | 24.1 | 3.76 | 2.83 | 2.20 | |
| | 11/ 3/41 | 1.8 | 20.6 | 4.41 | 3.97 | 2.48 | |
| | 11/24/41 | 1.3 | 15.0 | 4.28 | 1.76 | 2.43 | |
| | 10/12/43 | 0.2 | 8.8 | 4.95 | 2.11 | 3.67 | |
| 3 . . . | 11/17/41 | 22.0 | 26.3 | 3.44 | 3.07 | 0.89 | 2 |
| | 11/24/41 | 4.4 | 13.8 | 4.05 | 2.08 | 1.86 | |
| | 12/ 1/41 | 2.4 | 22.2 | 3.75 | 2.65 | 1.06 | |
| | 12/ 8/41 | 1.0 | 12.9 | 4.17 | 2.38 | 2.31 | |
| 4 . . . | 4/ 7/42 | 35.0 | 26.6 | 3.11 | 3.00 | 0.44 | 8 |
| | 4/14/42 | 26.0 | 19.0 | 3.61 | 2.66 | 0.65 | |
| | 4/21/42 | 7.5 | 15.0 | 3.20 | 3.38 | 1.11 | |
| | 4/28/42 | 3.0 | 13.2 | 4.11 | 3.22 | 0.60 | |
| | 5/ 4/42 | 3.0 | 12.8 | .. | .. | 0.74 | |
| | 5/12/42 | 1.4 | 11.1 | 3.88 | 2.86 | 0.92 | |
| | 7/27/42 | 0.2 | 9.8 | 3.94 | 4.20 | 1.20 | |
| 5 . . . | 7/ 1/42 | 15.0 | 30.3 | 2.70 | 3.87 | 0.68 | 4 |
| | 7/ 7/42 | 9.0 | 36.4 | 2.87 | 4.35 | 0.53 | |
| | 7/15/42 | 2.7 | 18.1 | 3.59 | 4.65 | 0.83 | |
| | 7/22/42 | 1.8 | 22.2 | 3.85 | 3.27 | 0.79 | |
| | 7/29/42 | 1.8 | 20.4 | 4.45 | 3.80 | 1.39 | |
| | 8/ 7/42 | 0.6 | 22.3 | 4.11 | 2.54 | 1.56 | |
| | 8/13/42 | 0.6 | 24.4 | 3.71 | 2.77 | 0.92 | |
| | 8/19/42 | 0.4 | 17.1 | 4.38 | 3.18 | 1.72 | |
| | 8/26/42 | 0.5 | 19.0 | 3.88 | 3.65 | 1.84 | |
| | 9/28/42 | 0.2 | 12.5 | 3.82 | 2.97 | 2.01 | |
| 6 . . . | 7/10/42 | 20.0 | 25.6 | 3.90 | 2.92 | 0.16 | 2 |
| | 7/15/42 | 20.0 | 35.1 | 3.19 | 3.20 | 0.28 | |
| | 7/22/42 | 18.0 | 34.4 | 3.85 | 3.14 | 0.64 | |
| | 7/29/42 | 18.0 | 36.6 | 4.11 | 3.34 | 0.84 | |
| | 8/ 7/42 | 10.0 | 26.6 | 4.89 | 2.73 | 0.98 | |
| | 8/13/42 | 3.0 | 24.4 | 4.39 | 2.58 | 0.92 | |
| | 8/19/42 | 2.6 | 19.3 | 5.30 | 2.93 | 1.45 | |
| | 8/28/42 | 1.8 | 19.2 | 4.63 | 4.05 | 1.72 | |
| | 10/19/43 | 1.3 | 14.2 | .. | .. | 2.26 | |
| | 4/24/44 | 0.4 | 20.3 | 4.62 | 2.57 | 1.80 | |
| 7 . . . | 1/27/43 | 10.0 | 17.1 | 4.01 | 2.97 | 1.66 | 4 |
| | 2/ 4/43 | 5.5 | 13.0 | 3.88 | 3.04 | 2.62 | |
| | 2/10/43 | 3.5 | 12.5 | 4.19 | 3.17 | 2.66 | |
| | 10/19/43 | 0.6 | 7.8 | .. | .. | 4.44 | |
| 8 . . . | 5/29/43 | 16.5 | 23.5 | .. | .. | 2.52 | 1 |
| | 6/ 2/43 | 18.0 | 20.8 | .. | .. | 1.66 | |
| | 6/ 4/43 | 22.0 | 23.5 | .. | .. | 1.38 | |
| | 6/10/43 | 22.0 | 26.3 | | | | |
| | 6/14/43 | 21.0 | 30.7 | .. | .. | 0.48 | |
| | 6/21/43 | 16.0 | 23.2 | .. | .. | 1.31 | |
| | 6/28/43 | 6.0 | 24.7 | .. | .. | 1.33 | |
| | 7/ 3/43 | 5.3 | 23.8 | .. | .. | 1.77 | |
| 9 . . . | 6/28/43 | 16.0 | 15.0 | .. | .. | 0.70 | 1 |
| | 7/ 3/43 | 15.0 | 29.8 | .. | .. | 0.67 | |
| | 7/10/43 | 3.5 | 26.3 | .. | .. | 1.54 | |
| | 10/26/43 | 0.2 | 23.2 | 5.04 | 2.02 | 3.36 | |

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TABLE 4.—(*Continued.*)

| Case No. | Date | Per 100 cc. of plasma | | | | Urine benzoic A (gm. in 4 hrs.) | Duration of jaundice (wks.) on admission |
|---|---|---|---|---|---|---|---|
| | | Bilirubin (mg.) | Levulose (mg.) | Alb. (gm.) | Glob. (gm.) | | |
| 10 | 7/ 9/43 | 20.0 | 28.9 | .. | .. | 1.18 | 2 |
| | 7/13/43 | 28.0 | 31.7 | 3.71 | 3.52 | 1.16 | |
| | 7/20/43 | 18.0 | 24.1 | .. | .. | 1.46 | |
| | 7/28/43 | 7.0 | 18.0 | .. | .. | 2.29 | |
| | 8/27/43 | 0.2 | 13.6 | .. | .. | 2.61 | |
| | 10/24/43 | 0.3 | 14.7 | 5.11 | 2.91 | 3.04 | |
| 11 | 5/14/43 | 16.0 | 28.5 | 3.59 | 2.84 | 1.09 | 1 |
| | 5/17/43 | 13.0 | 16.4 | .. | .. | 2.05 | |
| | 5/21/43 | 8.0 | 17.2 | .. | .. | 2.14 | |
| 12 | 7/13/43 | 10.0 | 9.1 | .. | .. | 3.59 | 1 |
| | 7/18/43 | 7.0 | .. | .. | .. | 2.76 | |
| | 7/21/43 | 3.0 | 10.2 | .. | .. | 3.57 | |
| 13 | 2/18/43 | 15.0 | 29.0 | 4.07 | 3.45 | 0.72 | 10 |
| | 11/ 2/43 | 0.2 | 13.1 | 4.88 | 3.37 | 3.51 | |
| 14 | 9/15/42 | 16.0 | 25.0 | 3.66 | 3.81 | 0.47 | 3 |
| | 9/22/42 | 12.5 | 26.3 | 4.56 | 3.19 | 0.69 | |
| | 9/29/42 | 6.5 | 14.9 | 4.81 | 3.63 | 1.20 | |
| | 10/ 6/42 | 4.5 | 12.5 | 4.52 | 2.70 | 2.38 | |
| 15 | 5/ 6/43 | 15.0 | 19.5 | 3.63 | 3.39 | 1.98 | 1 |
| | 5/12/43 | 15.0 | 24.3 | 3.62 | 3.19 | 2.05 | |
| | 5/20/43 | 5.0 | 15.2 | | | | |
| | 5/27/43 | 3.2 | 13.8 | .. | .. | 1.10 | |
| | 10/28/43 | 0.3 | 10.2 | 4.50 | 2.75 | 3.18 | |
| 16 | 7/16/43 | 14.0 | 26.6 | 4.09 | 4.05 | 0.75 | 1 |
| | 7/21/43 | 10.0 | 24.1 | .. | .. | 1.76 | |
| | 7/27/43 | 4.0 | 15.5 | .. | .. | 2.04 | |
| 17 | 11/17/43 | 12.0 | 20.8 | 2.85 | 3.91 | 0.86 | 1 |
| | 11/24/43 | 12.0 | 22.7 | 3.41 | 4.96 | | |
| | 12/ 7/43 | 5.0 | 13.2 | 4.45 | 5.79 | 1.34 | |
| | 12/24/43 | .. | .. | .. | .. | 3.71 | |
| 18 | 8/11/43 | 15.0 | 20.8 | 4.09 | 3.56 | 0.77 | 3 |
| | 8/18/43 | 8.0 | 17.4 | | | | |
| | 8/25/43 | 3.6 | 12.5 | .. | .. | 1.83 | |
| 19 | 8/ 4/43 | 17 0 | 29.4 | 3.84 | 3.72 | 0.75 | 1 |
| | 8/16/43 | 10.0 | 18.2 | .. | .. | 1.12 | |
| | 8/24/43 | 4.5 | 13.3 | .. | .. | 1.92 | |
| 20 | 4/ 3/42 | 8.8 | 14.3 | 3.59 | 2.74 | 1.16 | 8 |
| | 4/16/42 | .. | 14.8 | 4.63 | 2.83 | 2.06 | |
| | 4/24/42 | 3.0 | 9.5 | 3.94 | 2.74 | 2.82 | |
| 21 | 12/18/42 | 7.0 | 19.0 | 4.23 | 3.40 | 1.57 | 2 |
| | 12/28/42 | 1.2 | 13.9 | 4.11 | 4.69 | 1.35 | |
| | 10/16/43 | 0.2 | 10.6 | .. | .. | 3.01 | |
| 22 | 5/14/43 | 8.0 | 19.2 | 3.75 | 3.18 | 2.23 | 1 |
| | 5/17/43 | 3.0 | 14.0 | .. | .. | 2.47 | |
| | 5/21/43 | 0.2 | 12.9 | .. | .. | 3.71 | |
| 23 | 12/ 1/41 | 9.0 | 20.0 | 3.76 | 3.75 | 2.46 | 1 |
| | 12/17/41 | 0.7 | 7.1 | 5.24 | 1.90 | 2.22 | |
| | 12/10/43 | 0.2 | 8.3 | 5.06 | 2.52 | 2.91 | |
| 24 | 5/29/43 | 9.0 | 16.5 | .. | .. | 2.52 | 1 |
| | 6/ 2/43 | 4.0 | 10.0 | .. | .. | 2.27 | |
| | 6/ 4/43 | .. | .. | .. | .. | 2.79 | |
| | 6/12/43 | .. | .. | .. | .. | 2.82 | |

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TABLE 4.—(*Continued.*)

| Case No. | Date | Per 100 cc. of plasma | | | | Urine benzoic ā (gm. in 4 hrs.) | Duration of jaundice (wks.) on admission |
|---|---|---|---|---|---|---|---|
| | | Bilirubin (mg.) | Levulose (mg.) | Alb. (mg.) | Glob. (mg.) | | |
| 25 . . . | 6/ 2/41 | 6.0 | 14.5 | 3.88 | 2.46 | 1.34 | 1 |
| | 11/ 9/43 | 0.2 | 15.4 | 4.51 | 3.01 | 3.41 | |
| 26 . . . | 6/26/41 | 2.0 | 12.6 | 3.75 | 3.79 | 2.03 | 5 |
| 27 . . . | 6/17/41 | 2.0 | 9.3 | 3.58 | 4.15 | 1.52 | 6 |
| 28 . . . | 8/31/42 | 3.8 | 8.4 | 3.75 | 3.06 | 1.69 | 1 |
| 29 . . . | 12/10/42 | 1.7 | 15.4 | 3.49 | 3.83 | 2.79 | 1 |
| 30 . . . | 12/16/42 | 1.0 | 16.6 | 4.23 | 3.14 | 3.66 | 2 |
| 31 . . . | 5/28/42 | 6.0 | 9.3 | 3.79 | 3.60 | 3.12 | 1 |
| 32 . . . | 12/7/42 | 0.7 | 11.5 | 4.49 | 2.91 | 3.19 | 1 |
| | 11/23/43 | 0.2 | 9.7 | 5.13 | 2.68 | 3.06 | |
| 33 . . . | 12/22/41 | 2.0 | 12.3 | 5.29 | 2.92 | 2.47 | 2 |
| 34 . . . | 2/21/42 | 5.8 | 10.9 | 3.34 | 3.09 | 2.58 | 1 |
| 35 . . . | 2/ 4/43 | 3.5 | 11.8 | 4.65 | 1.99 | 2.96 | 1 |
| 36 . . . | 9/21/43 | 7.2 | 16.2 | 4.67 | 2.66 | 2.42 | 1 |
| 37 . . . | 10/12/43 | 4.5 | 18.0 | 3.93 | 3.23 | 2.62 | 2 |
| | 12/16/43 | 0.3 | 11.2 | 4.54 | 2.53 | 2.53 | |
| 38 . . . | 9/13/43 | 3.3 | 9.0 | 4.29 | 2.58 | 2.12 | 1 |
| | 12/19/42 | 0.3 | 10.8 | 4.28 | 2.98 | 3.08 | |
| 39 . . . | 5/24/43 | 3.0 | 15.9 | .. | .. | 1.28 | 1 |

When plasma bilirubin was greater than 10 mg. per 100 ml., hippuric acid synthesis and levulose tolerance were invariably impaired and plasma albumin invariably below normal. Beyond this no clear-cut quantitative relationship could be made out between any of these tests performed on admission and the degree of liver damage as shown by the duration of the illness. Repeated tests, however, on 23 of the more severe cases showed clearly that the functions tested very often had not returned to normal at the time of dismissal (Table 5). In 10 patients, jaundice had disappeared and in 13 was minimal or slight, but the plasma bilirubin was still above normal in 20.

TABLE 5.—RESULTS OF TESTS AT THE TIME OF DISMISSAL (23 PATIENTS)

| | No. of cases |
|---|---|
| Hippuric acid synthesis impaired . . . . . | 13 |
| Levulose tolerance impaired . . . . . | 7 |
| Plasma bilirubin > 0.6 mg. per 100 ml. . . . . | 20 |
| Plasma bilirubin > 2 mg. per 100 ml. . . . . | 13 |

Plasma albumin and globulin, estimated in 13 patients on dismissal, were abnormal in 6 and 7 respectively.

An attempt was made to reëxamine all the patients and repeat the tests, but for several reasons the results have been unsatisfactory. Of the 39 patients, 15 were in the Forces and have been lost sight of: some have been directed to work elsewhere and travel difficulties have

made others unwilling to come for examination. Data from 15 patients only have been obtained. On dismissal from hospital all but 1 of these (Case 10) showed slight jaundice and abnormality of one or more hepatic function tests. When examined 4 weeks to 29 months later, all the patients said they felt well and none showed jaundice or other evidence of hepatic disease. Hippuric acid synthesis, levulose tolerance, plasma proteins and bilirubin were within normal limits in 9 cases (Cases 2, 7, 10, 15, 21, 23, 32, 37 and 38, Table 4), but one or more tests were abnormal in 6 patients (Cases 4, 5, 6, 9, 13 and 25, Table 6).

TABLE 6.—IMPAIRMENT OF HEPATIC EFFICIENCY PERSISTING AFTER DISMISSAL FROM HOSPITAL

| Case No. | Per 100 ml. of plasma | | | | Urine benzoic ā (gm. in 4 hrs.) | Time since dismissal from hospital (mos.) |
|---|---|---|---|---|---|---|
| | Bilirubin (mg.) | Levulose (mg.) | Alb. (gm.) | Glob. (gm.) | | |
| 4 | 0.2 | 9.8 | 3.94 | 4.20 | 1.20 | 2½ |
| 5* | 0.2 | 12.5 | 3.82 | 2.97 | 2.01 | 1 |
| 6 | 1.3 | 14.2 | .. | .. | 2.26 | 14 |
| 6 | 0.4 | 20.8 | 4.62 | 2.57 | 1.80 | 20 |
| 9 | 0.2 | 23.2 | 5.04 | 2.02 | 3.36 | 3 |
| 13 | 0.2 | 13.1 | 4.88 | 3.37 | 3.51 | 9 |
| 25 | 0.2 | 15.4 | 4.51 | 3.01 | 3.41 | 29 |

* Now in A.T.S.; well; time since dismissal from hospital, 14 months.

The period of observation was short (Cases 4, 5 and 9) or the abnormalities were slight (Cases 13 and 25), but in Case 6 there was well-marked impairment of both levulose tolerance and hippuric acid synthesis in a patient without jaundice, 20 months after the attack of acute infective hepatitis.

INFECTIVE HEPATITIS—SUBACUTE AND CHRONIC STAGE. While clinical manifestations of subacute hepatitis or cirrhosis (chronic hepatitis) have not so far been observed in the 39 acute cases described, during the past 18 months 4 patients have been seen with striking hepatic lesions believed to be sequels to acute infective hepatitis (Cases 40 to 43, Table 7). Specimens for histologic examination were obtained either at operation or postmortem examination, and liver efficiency tests showed marked impairment of function in all the cases (Table 7).

**Case Reports.** CASE 40. A woman of 56 who in October 1943 developed marked anorexia and nausea. About 4 weeks later her friends remarked she was jaundiced. Jaundice became rapidly worse and persisted, although the patient thought it fluctuated in intensity. On admission to hospital in December 1943 jaundice was marked and on deep inspiration a firm smooth swelling was palpable under the right costal margin towards the midline. At laparotomy the pancreas and ducts were normal and the mass was the deeply pigmented liver. Biopsy showed great disorganization of the liver with no sign of resolution. When she was discharged from hospital, Jan. 23, 1944, jaundice was much less but the liver was still palpable and there was slight edema of the ankles. On February 16 she was readmitted because of sudden intense dyspnea and cyanosis. Her condition had deteriorated, the liver was larger, the spleen was palpable and there was ascites and considerable edema. The dyspnea was due to a very large right-sided pleural effusion. After paracentesis and salt and fluid restriction she improved and was dismissed from hospital on March 25. She died at home of hematemesis on April 20. No autopsy was made.

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CASE 41. A soldier 21 years old who developed jaundice after some days of anorexia and vomiting. Numerous cases of jaundice were occurring at this time in his unit. On 2 occasions when jaundice had almost gone a relapse occurred. When admitted to hospital on Aug. 16, 1941, he had been jaundiced for 8 months. Liver dullness was diminished. The spleen was not palpable. Subsequently he was transferred to a military hospital where a laparotomy was performed. The pancreas and ducts were normal and the liver was the seat of cirrhosis. Biopsy of the liver confirmed this diagnosis. He was discharged from the Army in "fair" condition and his further history is unknown.

CASE 42. A healthy woman of 24 who in February 1939 developed anorexia, nausea, vomiting and pain in the epigastrium. Within a few days deep jaundice appeared. When this had lasted 5 months a laparotomy was performed. The bile ducts and pancreas were normal. The liver was slightly enlarged, firm and deeply pigmented. Biopsy showed healing hepatitis and early cirrhosis. The jaundice is said to have gradually disappeared and she was well save for "dyspepsia" until January 1941 when she had a slight hematemesis. In May 1941 pain in the epigastrium recurred followed by jaundice and swelling of the abdomen. On admission to this unit on June 13, 1941, there was marked jaundice and ascites. The liver was much enlarged and the spleen moderately so. Hematemesis recurred on several occasions and she died on July 12. Postmortem examination showed cirrhosis of the liver. Esophageal varices were present. Histologic examination of the liver showed well-established multilobular cirrhosis.

CASE 43. A healthy woman who in August 1942 developed jaundice after some days of epigastric discomfort, nausea and loss of appetite. When seen in hospital in November 1942 jaundice was still present, though less marked, and the liver was palpable. At laparotomy both liver and spleen were slightly enlarged. The bile ducts and pancreas were normal. Hepatic biopsy showed a mild degree of cirrhosis. When next seen in May 1943 the liver was now larger and veins were prominent on the abdominal wall. Hematemesis occurred on 2 occasions. She was re-admitted in July 1943 with severe hematemesis, from which she died. At autopsy cirrhosis of the liver with esophageal varices was found. Terminal miliary tuberculosis with infiltration of the stomach and esophagus complicated the picture. Two other patients (Cases 44 and 45) are also believed to have sustained persisting hepatic damage from an attack of acute infective hepatitis. Their illnesses also dated from a severe attack of jaundice and 1 of them has shown slight jaundice for 2 years since. Histologic confirmation of a hepatic lesion was not obtained, but both patients showed marked hepatic dysfunction.

CASE 44. A healthy man of 38 who in December 1941 developed nausea and flatulence which were followed in a few days by jaundice which was intense for 20 weeks. After this it persisted in very slight degree and he suffered from flatulent dyspepsia. In April 1943, after an attack of epigastric pain, jaundice became more marked and the stools pale for 3 weeks. Since that time there was slight jaundice, which, on admission to hospital in March 1944, was minimal. The liver and spleen were not enlarged. Blood picture and erythrocyte fragility were normal. Barium meal and enema were normal.

CASE 45. A healthy woman who in 1939 had a severe attack of jaundice lasting 4 months and during which ascites was said to have been present. Since that time there has been no jaundice and her only complaint was of being easily tired. In April 1943 she began to vomit after meals and was drowsy and irritable. On admission to hospital on April 17, 1943, there was no jaundice. Liver and spleen were not palpable. Barium meal and barium enema were negative. She improved rapidly and was dismissed symptom-free in 2 weeks.

The results of the liver efficiency tests are shown in Table 7. Plasma bilirubin was above normal in all cases but bore no relation to the severity of the condition, in Case 40 for example, falling as the patient's

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condition steadily deteriorated. Levulose tolerance, hippuric acid synthesis and plasma albumin and globulin were abnormal in all the cases.

TABLE 7.—LIVER FUNCTION TESTS IN SUBACUTE HEPATITIS AND CIRRHOSIS DEVELOPING AFTER AN ATTACK OF ACUTE INFECTIVE HEPATITIS

| Case No. | Date | Per 100 ml. of plasma | | | | Urine benzoic á (gm. in 4 hrs.) |
|---|---|---|---|---|---|---|
| | | Bilirubin (mg.) | Levulose (mg.) | Alb. (gm.) | Glob. (gm.) | |
| 40 . . . | 1/12/44 | 15.0 | 28.1 | 2.79 | 4.91 | 0.63 |
| | 2/17/44 | 5.0 | 43.4 | 2.66 | 5.08 | 0.55 |
| | 3/24/44 | 1.3 | 40.0 | 3.25 | 4.01 | 0.53 |
| 41 . . . | 6/28/41 | 12.0 | 34.0 | 2.62 | 6.22 | 0.61 |
| 42 . . . | 6/25/41 | 12.0 | 16.1 | 2.92 | 3.67 | 1.58 |
| 43 . . . | 12/16/42 | 5.0 | 26.3 | 2.98 | 3.56 | 1.53 |
| | 1/ 7/43 | 8.0 | 32.5 | 3.11 | 4.41 | 1.50 |
| | 2/ 4/43 | 8.0 | 50.0 | 2.97 | 4.19 | 1.10 |
| | 2/11/43 | 4.0 | 41.6 | 2.84 | 3.56 | 1.00 |
| | 3/11/43 | 5.0 | 40.0 | 2.50 | 4.46 | 1.10 |
| | 5/24/43 | 7.0 | 30.7 | .. | .. | 0.69 |
| 44 . . . | 3/ 3/44 | 2.0 | 36.3 | 3.83 | 4.90 | 1.91 |
| 45 . . . | 4/13/43 | 0.8 | 26.0 | .. | .. | 1.36 |

**Discussion.** The number of cases studied in the early acute stage is too small to draw conclusions regarding the value of any clinical manifestation in assessment of prognosis, particularly as none of the patients died. It can be said, however, that jaundice which at its height was intense often lasted many weeks, but jaundice which was slight or moderate cleared up in 2 or 3 weeks.

The liver efficiency tests showed that even comparatively moderate attacks of acute infective hepatitis generally produced an initial impairment of all the hepatic functions investigated. One major objection commonly raised against the use of hepatic efficiency tests is that they are unlikely to be positive unless death is imminent from cholemia, so great is the hepatic reserve. Surely there is enough evidence from recently developed tests to refute this once and for all. It is also apparent that the functional impairment sometimes persisted after jaundice had gone or was minimal and even when the plasma bilirubin was within normal limits. One patient with a plasma bilirubin of 0.4 mg. per 100 ml., although clinically normal and feeling well, still showed definite impairment of hippuric acid synthesis and levulose tolerance 20 months after dismissal. Even from this single case it is justifiable to conclude that a latent chronic hepatitis can occur after an attack of acute infective hepatitis.

Further evidence of residual hepatic damage after an attack of acute infective hepatitis is afforded by 6 cases which were admitted to the wards during the 2 years of this investigation. In each case the illness started with intense, prolonged jaundice for which no known hepatotoxic agent was found responsible. One soldier patient developed jaundice during an epidemic in his unit. The existence of subacute or chronic hepatitis was confirmed by histologic examination of

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4 patients, from specimens obtained at operation or autopsy. The hepatic functions investigated were grossly impaired in all. The rate of progress of the lesion varied considerably, 1 patient dying in 5 months from the onset of the jaundice and 2 others in 2 years, hematemesis being the direct cause of death. Two patients, 1 of whom still shows minimal jaundice, are leading active lives and show no gross evidence of hepatic disease, although tests show that hepatic dysfunction persists. The sixth patient has been lost sight of.

Space forbids a discussion on the relationship of the condition of the liver to the plasma proteins. A fall in albumin and a rise in globulin were encountered frequently, but since changes of the order noted in cases of acute infective hepatitis occur in many non-hepatic conditions, the test cannot be considered a specific one. More marked changes in both fractions were observed in 6 out of the 7 patients with persistent hepatic damage.

The result of this small investigation gives no answer to the question whether persisting hepatic damage is frequent after an attack of acute infective hepatitis, but gives further indication that it does occur. From the 7 examples recorded here it would seem that the condition may be clinically obvious or latent, for a time at least, and detectable only by hepatic function tests. With the records available of those who have had the disease while serving in the Forces, it should not be difficult to reach a definite conclusion by a "follow up" on a large scale.

**Summary.** 1. The occurrence and detection of residual damage to the liver after an attack of acute infective hepatitis is discussed.

2. The clinical manifestations shown by 39 patients with acute infective hepatitis are described. None died and all left hospital well or with slight jaundice only. There was a direct relationship between the depth of the jaundice and its duration, inconstant insofar as deep jaundice occasionally cleared rapidly. A biopsy was made on 1 case.

3. Hippuric acid synthesis, levulose tolerance and the estimation of plasma albumin, globulin and bilirubin were used as tests for liver damage.

4. Hippuric acid synthesis and levulose tolerance were impaired and plasma albumin invariably reduced when the plasma bilirubin was greater than 10 mg. per 100 ml., less constantly with a slighter degree of bilirubinemia.

5. Tests repeated at the time of dismissal showed that one or more functions were still abnormal in a large proportion of 23 patients.

6. Six out of 15 patients reëxamined 4 weeks to 29 months after dismissal still showed abnormality of one or more hepatic function, although all felt well and showed no clinical evidence of hepatic disease. Plasma bilirubin was within normal limits in all cases. One patient showed well-marked impairment of levulose tolerance and hippuric acid synthesis 20 months after the acute attack.

7. The history, physical signs and results of liver function tests are discussed in 6 patients with hepatic disease believed to be a sequel to acute infective hepatitis. Autopsy or biopsy was made in 4 and confirmed the existence of subacute hepatitis or cirrhosis.

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For the interpretation of the histology in Cases 2, 40, 42 and 43, I am indebted to Dr. Alan C. Lendrum of the Department of Pathology, University of Glasgow. My thanks are also due to Prof. J. W. McNee for his criticisms and advice.

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# ORAL ADMINISTRATION TO VOLUNTEERS OF FECES FROM PATIENTS WITH HOMOLOGOUS SERUM HEPATITIS AND INFECTIOUS (EPIDEMIC) HEPATITIS*

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Transmission experiments in human volunteers[1,2] have shown that the causative agent of *infectious* (*epidemic*) *hepatitis* may be present in the feces of persons with the active disease. It has seemed desirable, therefore, to determine if the causative agent of *homologous serum hepatitis* is present in the feces of persons with this disease. In the present report of transmission experiments in human volunteers, the effects of the oral administration of feces obtained from patients with homologous serum hepatitis are compared with those obtained by

* This investigation was conducted under the Commission on Measles and Mumps, Board for the Investigation and Control of Influenza and Other Epidemic Diseases in the Army, Preventive Medicine Service, Office of the Surgeon General, U. S. Army, Washington, D. C.

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administration of feces from patients with infectious (epidemic) hepatitis. The results of a preliminary study on the length of time the agent of infectious hepatitis persists in feces also are presented.

**Materials and Methods.** *Source of Material.* Feces specimens used in the investigation were obtained from two sources: (1) From volunteers with hepatitis induced by experimental inoculation with an icterogenic mumps convalescent plasma.[3] (2) (*a*) From patients with hepatitis contracted during a spontaneously occurring epidemic of infectious hepatitis;[4] (*b*) from volunteers who developed hepatitis following experimental ingestion of feces obtained from the patients mentioned under (*a*). All specimens were frozen within 24 to 48 hours after collection and stored at −5 to −20° C.

*Preparation of Specimens for Inoculations.* The specimens to be pooled were partially thawed and portions of each were placed in a common receptacle. The mixture was subjected to the action of a Waring Blendor or an electric stirrer, distilled water being added in amount sufficient to give a fluid suspension. The homogenous suspension was then strained through 2 to 4 layers of gauze. The resulting preparations represented 10 to 50% suspensions of feces in distilled water, the concentration depending upon the water content of the original specimens. The preparations were kept at −5 to −20° C. until used in the experiments to be described. Bacteriologic examination of the individual specimens and of the final pooled preparations revealed no pathogenic bacteria.

Homologous Serum Hepatitis Feces Specimens. The following 3 pools were prepared from specimens obtained from volunteers in various stages of the disease:

1. *Pool 1 FSH.* This was composed of portions of all feces specimens obtained from volunteer B. C. during the first 5 days after the appearance of jaundice.

2. *Pool 2 FSH.* This was composed of: (*a*) Pool 1 FSH plus equal volumes of (*b*) a pool of all specimens obtained from volunteer C. L. during the first 10 days after the appearance of jaundice plus (*c*) a pool of all specimens obtained from volunteer F. S. during the 7 day period immediately preceding visible jaundice and during the first 5 days after the appearance of jaundice. The final pool (2FSH) thus included portions of all specimens obtained from 1 volunteer during the pre-icteric stage and from 3 volunteers during the early icteric stage.

3. *Pool 3 FSH.* This was prepared by pooling portions of specimens obtained from: (*a*) Volunteer D. C., 4, 8 and 18 days after the appearance of jaundice, (*b*) volunteer C. E., 5 and 9 days after the appearance of jaundice, and (*c*) volunteer C. K., 2 and 5 days after the appearance of jaundice.

Infectious (Epidemic) Hepatitis Feces Specimens. The following 3 pools were prepared from specimens obtained from patients in various stages of this disease:

1. *Pool 1 FIH.** This was prepared by pooling portions of specimens obtained from: (*a*) Patient R. G. on the 1st day that jaundice was visible, (*b*) patient M. Z., 3 days after jaundice had appeared, (*c*) patient R. Go., 9 days after the onset of infectious hepatitis without jaundice, and (*d*) patient H. G., 12 days after the onset of infectious hepatitis without jaundice.

2. *Pool 2 FIH.* This was prepared by pooling all feces specimens obtained from 2 volunteers (W. M., R. R. M.) during the pre-icteric, early icteric and mid-icteric stages of the disease resulting from the experimental ingestion of Pool 1 FIH.

3. *Pool 3 FIH.* This was prepared by pooling portions of the specimens obtained from the same 2 volunteers (W. M., R. R. M.) 3 weeks after disappearance of jaundice.

*Method and Route of Inoculation.* All of the pooled feces preparations were either diluted with milk (or chocolate milk) and then ingested or were injected

* A Seitz filtrate of this pool injected into mice, guinea pigs, and monkeys, showed evidence of no other agent pathogenic for man.

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into the stomach through a gastric tube. No adverse effects were noted during the immediate post-inoculation period.

*Laboratory Studies on Volunteers.* Liver function and certain other studies, using methods previously described,[3] were carried out at frequent intervals before and after the ingestion of the feces preparations.

**Results.** The volunteers receiving Pools 1, 2 and 3 FSH, which were prepared from feces that had been obtained from patients during the pre-icteric and icteric stages of *homologous serum hepatitis*, have been observed for 10, 7 and 4 months respectively. As shown in Table 1, none of these volunteers developed evidence of hepatitis during the period of observation. In contrast, 6 of 12 men inoculated with Pool 1 FIH, prepared from feces that had been obtained from patients with *infectious hepatitis*, contracted the disease, all within 26 days after inoculation.

TABLE 1.—RESULTS OF ORAL ADMINISTRATION OF FECES OBTAINED FROM PATIENTS WITH HOMOLOGOUS SERUM HEPATITIS AND INFECTIOUS (EPIDEMIC) HEPATITIS TO VOLUNTEERS

| Feces preparation | No. inoc. | Amt. (ml.) | Route | Results | | | |
|---|---|---|---|---|---|---|---|
| | | | | No. illness | Hepatitis: Without jaundice | Hepatitis: With jaundice | Incubation period (days) |
| Pool 1 FSH* | 11 | 4–12 | I-G† | 11 | 0 | 0 | |
| Pool 2 FSH | 3‡ | 15 | I-G | 3 | 0 | 0 | |
| Pool 3 FSH | 5 | 10 | Oral | 5 | 0 | 0 | |
| Pool 1 FIH§ | 2 | 5 | Oral | 0 | 0 | 2 | 21–25 |
| Pool 1 FIH | 10 | 2 | Oral | 6 | 1 | 3 | 20–26 |
| Pool 2 FIH | 7 | 10 | Oral | 6 | 0 | 1 | 26 |
| Pool 3 FIH | 7 | 10 | Oral | 7 | 0 | 0 | |

* FSH—Feces serum hepatitis.
† I-G—Intragastric, injected through gastric tube.
‡ These volunteers had received Pool 1 FSH 6 months previously. Since none of the 11 men receiving Pool 1 FSH developed hepatitis, these men were considered satisfactory for testing Pool 2 FSH.
§ FIH—Feces infectious (epidemic) hepatitis.

Pools 2 and 3 FIH were used in a preliminary attempt to determine how long the agent of infectious hepatitis continued to be excreted in the feces after recovery from the disease. One of 7 volunteers inoculated with Pool 2 FIH, representing specimens collected from the 2 patients during the active stage of the disease, developed hepatitis 26 days after inoculation. None of the 7 men inoculated with Pool 3 FIH, which was composed of specimens obtained from the same 2 patients 3 weeks after the disappearance of jaundice, developed hepatitis. Both groups have been observed for 3 months.

**Discussion.** In respect to the experiments with feces obtained from patients with homologous serum hepatitis, the pools used included many specimens from 6 different patients in various stages of the active disease. If this causative agent were commonly excreted in feces, it is probable that it would have been present in at least 1 of the 3 pools. All of the inoculated volunteers were presumably susceptible as judged by age (under 30), the absence of previous history of hepatitis, and the lack of clinical or laboratory evidence of hepatic disease. The systematic application of a group of liver function tests at least twice weekly made it improbable that a brief attack of hepatitis was overlooked. Thus, the failure of any of these men to show evidence of

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hepatitis suggests that the causative agent either was not present in the feces of these patients with homologous serum hepatitis or was not active when administered by the gastro-intestinal route. This observation offers a possible explanation for one of the puzzling differences between serum and infectious (epidemic) hepatitis, namely, the apparent failure of epidemics of hepatitis to originate from patients with serum hepatitis (other than those related to the injection of homologous blood products).

**Summary.** 1. Pooled specimens of feces from 6 subjects during various stages of homologous serum hepatitis were administered orally to 19 healthy volunteers. None of these subjects showed evidence of hepatitis during a 4 to 6 month period of observation, suggesting that the causative agent either was not present in the feces or was not active when administered by the gastro-intestinal route.

2. Pooled specimens of feces from patients with infectious (epidemic) hepatitis were administered orally to healthy volunteers. Hepatitis occurred within 26 days in 6 of 12 subjects, confirming the observation of others that the causative agent is present in the feces of patients with the active disease.

3. Pooled specimens of feces obtained from 2 volunteers during the pre-icteric and icteric stages of experimentally produced infectious (epidemic) hepatitis were administered orally to 7 healthy volunteers. One developed the disease after 26 days, indicating that the agent was present in feces obtained during the active disease. Pooled specimens of feces from the same 2 volunteers 3 weeks after the disappearance of jaundice also were administered orally to 7 healthy volunteers. None developed hepatitis during a 4 month period of observation suggesting that the agent was not present in the feces 3 weeks after the disappearance of icterus.

ACKNOWLEDGEMENT: This investigation was made possible by the coöperation of the Administrative Staffs of Selective Service, Camp Operations Division, The National Service Board for Religious Objectors, The American Friends Service Committee, the Philadelphia State Hospital, and the New Jersey State Hospital. Invaluable assistance was rendered by Capt. S. S. Gellis, M.C., A.U.S., Dr. F. D. W. Lukens, and by the members of our laboratory staff: Mr. Charles Ming, Mrs. Mary Ming, Miss Dorothy Feinberg, Miss Arvilla Howley and Mrs. Jean Flick. We are indebted to the staff of the William Pepper Laboratory of Clinical Medicine of the University of Pennsylvania for the bacteriologic studies, to Miss Anne Messer and Miss Mary Lanning of the Biochemical Laboratory of the Philadelphia General Hospital for some of the biochemical analyses, and to the members of the laboratory staff of the New Jersey State Hospital for their wholehearted coöperation in many ways.

The authors desire to express their appreciation of the contribution made by those members of Civilian Public Service Unit No. 140 (Philadelphia, Pa.) who served as experimental subjects and to the other members of that unit, many of whom assisted materially in the conduct of this investigation.

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# LYMPH NODES IN LEISHMANIASIS

## REPORT ON 2 CASES

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DESCRIPTIONS of kala azar state that the lymph nodes are frequently involved and the study of smears from excised posterior cervical or inguinal lymph nodes has been advocated as a diagnostic procedure by Cochran in 1912.[1] Kirk and Sati[5] were able to demonstrate Leishman-Donovan bodies by lymph node aspiration, in 30 consecutive cases of leishmaniasis. In a series of autopsies on 31 clinically proven cases of kala-azar, Hu[4] recovered parasites from the lymph nodes alone in 3 of the treated cases. No report has been found of patients with leishmaniasis presenting themselves with lymph node enlargement as the outstanding characteristic of the disease. In this connection a recent case of considerable interest is that reported by Lipscomb and Gibson[6] of a patient who developed visceral leishmaniasis in Malta. Tender epitrochlear cervical and inguinal lymph nodes were the only positive physical findings noted approximately 6 months before the diagnosis was established by sternal puncture, blood culture and lymph node biopsy. Smear and section of an inguinal node revealed numerous Leishmania. In reports of this disease in man little reference is made to the histopathologic picture of the lymph nodes; however, the microscopic picture in the lymph nodes of hamsters has been extensively described.[2,3,7]

Two soldiers recently arrived from the Mediterranean area were admitted to different U. S. Army hospitals in England, because of lymph node enlargement. No satisfactory explanation for this enlargement was found in either case, so that a cervical lymph node was removed from each patient and sent to this laboratory for histologic examination. Leishmania were demonstrated in the tissue from both, and the organism grown in culture from 1. Because of the diagnostic problem presented by the uncomplicated lymph node involvement and since we were able to obtain lymph nodes at intervals for detailed histologic study, these cases are reported.

**Case Reports.** CASE 1. A white male, air transport pilot, 22 years old, who had been in the service for 2 years, left the United States in May 1943, flew to Brazil, Dakar, and North Africa, was in Egypt for 1 week during August and in Sicily from September 1943 to January 1944. Native dogs entered the camp in Sicily. He arrived in England in February 1944, and entered a station hospital on March 7, stating that he had first noticed enlargement of the cervical lymph nodes on left side while in Sicily. Since then there had been progressive enlargement of the anterior and posterior cervical lymph



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nodes bilaterally, as well as axillary, inguinal and left epitrochlear nodes. There had been no other symptoms and he felt well, having gained 5 pounds in weight during the period. He consulted a medical officer because his neck was unsightly.

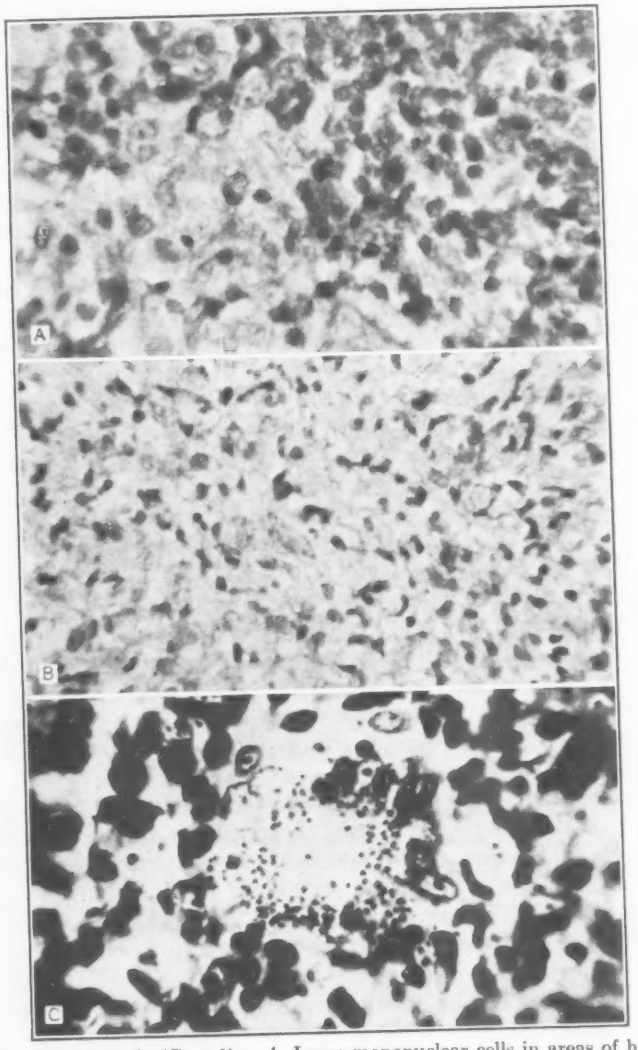


FIG. 1.—Lymph node (Case 1). *A*, Large mononuclear cells in areas of hyperplasia (× 800). *B*, Loose spongy edematous framework in focal areas, a moderate number of lymphocytes and neutrophils are present (× 440). *C*, Parasites in lymph nodes after the second biopsy. Tissue was formalin fixed, stained with Giemsa and rapidly decolorized (× 880).

*Physical examination* was negative except for the lymph node enlargement. The blood count was normal, the Kahn test and Widal reaction were negative, as were the heterophil antibody and *Br. abortus* agglutination reactions. Roentgenograms of chest and neck were negative. A cervical lymph node removed on March 7 presented considerable acute inflammation with numerous Leish-

mania. The patient was transferred to a general hospital for further study on March 25. At that time the posterior cervical, auricular and suboccipital lymph nodes were bean-sized or slightly larger, discrete and not tender. The epitrochlear nodes were palpable and the inguinals not remarkable. The spleen was not felt.

*Progress Notes.* The patient was asymptomatic during his stay in hospital. The red blood count was 4,800,000, hemoglobin 96%, and white blood cells 5000 (68% neutrophils). The total serum protein was 6.5 gm. % (albumin 4.8 and globulin 1.7). A sternal puncture performed on March 27 was negative for Leishmania, both on smear and culture. Aspiration of a posterior auricular lymph node was negative though the material obtained appeared to be mostly blood. Three days later a second posterior cervical lymph node was removed and smear, culture on NMN (Novy-MacNeal-Nicolle) medium, and histologic sections were all positive for Leishmania. Two hamsters were inoculated intraperitoneally with the culture. After 1 month, 1 was killed and Leishmania were found in the spleen and liver.

*Treatment* consisted of 15 daily injections of 6 cc. of sodium antimony gluconate to a total of 1800 mg. At the end of the course of treatment the patient was discharged with instructions for evaluation of therapy. A third lymph node was removed from the cervical region on May 26, and no Leishmania were found in the histologic section.

*Pathologic Anatomy.* The first lymph node removed was enlarged, measured 1.5 x 1.7 x 1.7 cm., hemorrhagic about the periphery, rather homogenous and relatively firm. *Microscopically*, the structure of the node was partially intact and the lymph follicles somewhat indistinct, because of cellular infiltration. There was extensive hyperplasia (Fig. 1 *A*) and in several areas near the periphery of the node, large monocytes were arranged in clusters around pink staining material. In such areas there were considerable numbers of Leishmania. The parenchymal network of the node was mottled by numerous focal lighter staining, spongy, edematous and necrotic areas (Fig. 1 *B*). Most of the parasites were in mononuclear cells; however, in many areas the cells had apparently ruptured and organisms were extracellular. The second node presented a somewhat similar histologic picture with numerous organisms (Fig. 1 *C*) and several of the more cellular areas replaced by large pink staining monocytes or "epithelioid" cells arranged in focal sheets. The third lymph node was of normal size with a slightly thickened capsule, and moderate hyperplasia with an occasional giant cell. A few granular bodies, but no parasites, were observed in the sections.

Case 2. Patient was a young adult male, admitted to hospital on Feb. 23, 1944. About 6 months previously, while in Sicily, the patient scraped the dorsum of his left hand against a wall, causing 2 abrasions. One healed promptly whereas the other became infected and did not heal for several weeks. Approximately 1 week after injury, a "sore" developed on the dorsum of the left wrist, which increased in size and resembled a carbuncle. Small amounts of pus escaped and the entire wrist was swollen, red streaks extended up the arm and tender nodules appeared in the left axilla. The abscess was incised and a considerable amount of pus evacuated. The red streaks and tender lymph nodes subsided, but the lesion did not heal and gradually ulcerated. The ulcer measured about 3.5 cm. across and healed after about 1 month. During this time, a smaller lesion that resembled a pimple developed on the left forearm. This also broke down, but healed within a short period. While in transit from North Africa in October 1943, he had a 3-day period of fever without chills. After a short time another lesion appeared on the posterior aspect of the right thigh, and a small tender ropy swelling was noted in the left groin, which gradually disappeared. Approximately 2 months before admission while shaving, the patient noticed a small lump behind the angle of the jaw on the right side. Other similar nodules appeared behind the left ear, and on the back of the neck. There had been no systemic symptoms, other than moderate anorexia and vomiting after meals on 2 occasions. The only significant findings were enlargement of

the posterior cervical lymph nodes and 1 large node at the angle of the jaw on the right. A few small firm shotty tender lymph nodes were felt in the inguinal region. The liver and spleen were not palpable. A large healed scar was present over the dorsum of the left wrist. The red blood count was

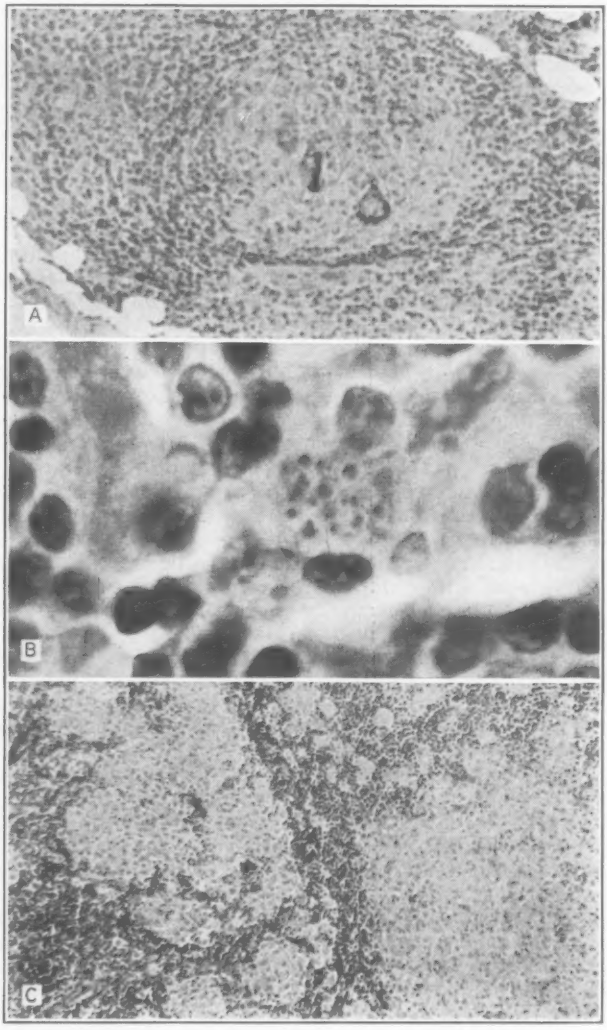


FIG. 2.—Lymph node (Case 2). *A*, Tubercle-like reaction in the perilymphatic tissues of the first lymph node removed (× 100). *B*, Cluster of parasites in loose stroma of the node (× 2000). *C*, Epithelioid cells replacing focal areas that previously contained organisms. No parasites were seen or cultured from lymph nodes with this histologic picture (× 50).

4,600,000, hemoglobin 90%, white blood cells 6500, with a normal differential. The Wassermann reaction and test for heterophil antibodies were negative. The patient was discharged from hospital on May 12, after receiving 6 cc. of sodium antimony gluconate twice daily for 7 days. One week after treatment, there were no palpable lymph nodes.

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*Pathologic Anatomy.* A lymph node removed from back of the neck about March 7, 1944, presented a granulomatous appearance with considerable fibrosis. In the perilymphatic tissues several multinucleated giant cells were observed in circumscribed areas of inflammation, resembling tubercles (Fig. 2 *A*). A few questionable Leishmania were seen in sections stained with H & E. In Giemsa stained tissues the structure of the parasites was accentuated (Fig. 2 *B*) so that a diagnosis of leishmaniasis was made. A second cervical lymph node was removed in April 1944. No organisms were seen on smear, and cultures on NMN medium were negative. Approximately half of the lymphoid tissue was replaced by homogenous sheets of pink staining epithelioid cells (Fig. 2 *C*). No organisms were demonstrated.

**Comment.** Although it is difficult to determine the exact date of onset of the disease in these cases, it is probable that both patients contracted it in Sicily or North Africa during the latter part of 1943. Both sought medical care at approximately the same time and the initial biopsy was performed on each case in March. The second lymph nodes were removed about 1 month later and in Case 1 a third node was removed 1 month after treatment began. In Case 2 the possibility of cutaneous leishmaniasis cannot be entirely excluded; however the history strongly suggests a pyogenic infection. The anatomic location of the involved lymph nodes does not indicate any relationship with the cutaneous infection on the hand. Sternal puncture was not done to determine whether there was generalized dissemination of the organisms, because the clinical picture did not indicate visceral leishmaniasis.

*Pathologic Anatomy.* During the preparation and examination of these tissues, several points of interest became evident. On routine examination with hematoxylin and eosin stain, these bodies may be easily overlooked unless one suspects their presence. In a section through an entire node there may be no organisms, whereas in other sections from the same paraffin block, they occur in large numbers. The necessity for cutting numerous sections is obvious. The apparently larger number and size of the parasites at the periphery of the node suggests that when fixation does not reach the organisms quickly they degenerate. This indicates the advisability of bisecting the node and preparing smears before the tissue is placed in fixative. Highly satisfactory preparations were obtained with Giemsa stain on formalin fixed tissues. Differentiation was short and sections carefully decolorized in resinous alcohol. The organisms appear as dark purplish blue bodies in sharp contrast to the pale gray of the phagocytic cells. If one wishes to accentuate the organisms as an aid in their detection, this can be accomplished by quick differentiation, sacrificing, of course, the cytology of the section (Fig. 1 *C*).

It is not possible with only 2 cases to reconstruct accurately the pathogenesis of the disease as it occurs in lymph nodes. Nevertheless certain similar features in both cases were observed, that seem worth considering in some detail. No sections of lymph nodes were available early in the disease, and the first biopsies were obtained presumably several months after the onset. At this time there is moderate fibrosis of the capsule, and the cortical lymph sinuses are filled with mono-

nuclear cells and lymphocytes. Although the lymph follicles are discernible they are relatively indistinct and there is considerable hyperplasia in the center of the follicles as well as of the reticular network of the node (Fig. 1 *A*). Throughout the pulp there are focal areas of decreased cellularity, which represent a spongy edematous stroma (Fig. 1 *B*) in which are scattered histiocytes. Leishmania are found most frequently in such sites, both intra- and extracellularly, in somewhat greater numbers near the periphery of the lymph node. In such areas there is a tendency to form multinucleated giant cells, in which organisms are fairly numerous. In one section the capsule of the node has apparently infiltrated and a granulomatous lesion with giant cells was observed in the perilymphatic tissue (Fig. 2 *A*). From the lymph nodes removed later, it appears that the spongy focal areas which contained organisms were infiltrated with and replaced by fairly compact sheets of pink staining epithelioid cells (Fig 2 *C*). Of the 2 instances where this extensive epithelioid reaction occurred, we were unable to detect organisms either by smear, cultures or histologic sections of the nodes.

**Summary.** Two cases of leishmaniasis are described in which the primary and most important symptom was enlargement of the cervical lymph nodes. Biopsy of lymph nodes made at intervals indicate certain features that should prove helpful in establishing the diagnosis, and separating this group of cases from other chronic granulomatous lesions of lymph nodes.

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## MITE OR SCRUB TYPHUS

### A Clinical and Laboratory Study of 64 Cases

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The purpose of this report is to present clinical and laboratory data on a disease encountered in this area which appears to be clinically and serologically identical with tsutsugamushi (Japanese river fever) also called mite or "scrub" typhus. Data are presented on 40 Chinese and 24 American soldiers who were admitted to this hospital during October, November and December of 1943 and January, 1944.

The presence of tsutsugamushi in Malaya was established by Dowden[3] in 1915. This was a typhus-like disease which differed from murine and louse-borne typhus chiefly in being transmitted by a mite

and in the Weil-Felix reaction which gave a high agglutination titer against proteus OXK and a negligible agglutination with OX2 and OX19. The clinical features of this disease included an abrupt onset, high fever, presence of a primary eschar, a maculo-papular rash occurring on the trunk, arms and legs, regional adenopathy in the area draining the site of the initial lesion, as well as generalized lymphadenopathy. The febrile illness usually lasted about 2 weeks and was followed by a lengthy convalescence marked chiefly by severe physical exhaustion. The disease was caused by a species of rickettsia. Subsequently a similar clinical picture, with the exception of the absence of a primary lesion, was described by Fletcher and Lesslar.[4] This was called rural typhus of Malaya and was thought to be different from tsutsugamushi because of the absence of a primary ulcer. As a result of extensive work by Lewthwaite[6] and his associates, it was shown that tsutsugamushi and rural typhus of Malaya were similar clinically, serologically and pathologically and that they had a common etiologic agent, namely *Rickettsia orientalis*. In this paper the disease will be referred to as mite typhus, the term "scrub" typhus being reserved for those cases of typhus-like disease in which the vector is not reasonably clear.[1,5] Recently, data obtained from autopsies on soldiers who served in the Buna-Gona campaign have been reported by Capt. Austin J. Corbett.[2]

**Procedure.** The 40 Chinese patients on whom careful and detailed clinical and laboratory observations were made, were admitted or transferred to a ward set aside for the study of this disease. Determinations of temperature, pulse and respiratory rate were made at 4-hour intervals. Daily blood pressure determinations were made. Weil-Felix reactions were run bi-weekly throughout the period of hospitalization which in most instances lasted 60 to 120 days. Determinations of blood urea nitrogen were made at bi-weekly intervals during the course of the fever. Complete blood counts (excluding erythrocytes) and urinalyses were made at weekly intervals. Each patient had a chest Roentgen ray on admission and also when a progress film was indicated. The films were interpreted by Lt. Col. P. J. Hodes. A weekly eye-ground examination was made by Capt. Harold G. Scheie. Physical examinations were made daily, concentrating especially on the appearance and distribution of rash, size of spleen and lymph nodes as well as other features pertinent to the particular case. Complete physical examinations were made and recorded every 3rd day during the early course of the disease and weekly during convalescence. Each of the Chinese had a lymph node removed for culture and microscopic study. The primary ulcer as well as portions of the skin from the site of the rash were excised in 15 cases. The results of the microscopic studies will be reported separately. In the preparation of some of the tables the duration of fever was used as the basis of comparison with other manifestations, but the duration of fever should not be considered an index of the severity of the illness. Reference to particular cases in the table will be made by numbers; Chinese 1 to 40; American 41 to 64.

**Results.** 1. INCUBATION PERIOD. The exact incubation period in the majority of instances could not be determined with certainty. The primary lesions were painless and as the troops frequently did not have an opportunity to examine their naked bodies, the time of development of the primary lesions could not be ascertained. All of the patients admitted having been in the jungle during the several weeks prior to the onset of the illness. In one American patient, in

whom the exact and only day of exposure to jungle vegetation was definitely known, the abrupt onset of his illness occurred 11 days later. The primary lesion on his arm was first noted 7 days after returning from the jungle.

TABLE 1.—LOCATION OF PRIMARY LESIONS

| Site | No. of cases |
|---|---|
| Anterior neck midline | 1 |
| Left side of neck, anterior | 2 |
| Suprasternal notch | 1 |
| Interscapular region | 1 |
| Axilla (right 7, left 6) | 13 |
| Right mammary area | 1 |
| Costal margin, anterior (right 2, left 5) | 7 |
| Costal margin, posterior (right 2 left 5) | 7 |
| Antecubital space (right) | 1 |
| Left wrist | 1 |
| Epigastrium | 1 |
| Left hypochondrium | 2 |
| Inguinal (right 1, left 1) | 2 |
| Left leg posterior | 1 |
| Right ankle | 2 |

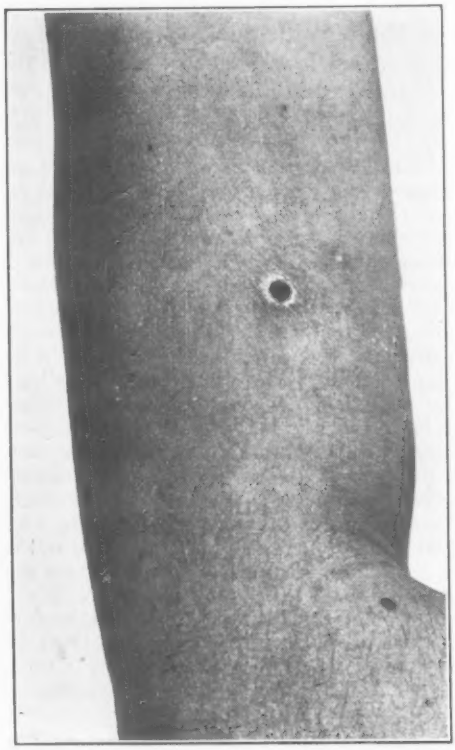

FIG. 1.—Primary ulcer on arm. Note black eschar.

2. PRIMARY ULCER. A typical primary ulcer was present in 43 out of 64 cases, an incidence of 67%. The most frequent sites of the ulcers were the upper trunk, particularly the axillæ and chest wall, anteriorly and posteriorly (Table 1). The initial lesion began as a red painless

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macule which in a few days became papular. A small excoriation then appeared on the dome of the papule which soon became deeper and

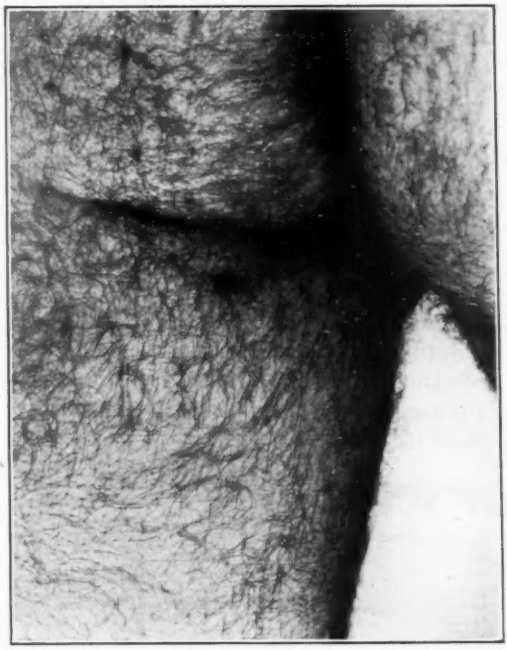

FIG. 2.—Primary ulcer on posterior aspect of left thigh.

FIG. 3.—Primary ulcer on scrotum with eschar lacking.

filled with a black eschar. (Figs. 1, 2 and 3.) Removal of the eschar left a punched-out ulcer. The typical lesion was about 5 to 7 mm. in diameter and 1 to 2 mm. deep. The average time of complete disappearance of the ulcer was on the 29th day of the disease (16 to 40 days).

3. Onset Symptoms. The onset was abrupt, with chills or chilliness, fever and headache being the most frequent symptoms. These were associated with malaise, generalized aching and marked anorexia and apathy. There was usually more than one chill, they occurred during the first 3 days and were not periodic or very severe. Cough was a prominent accompanying onset symptom in the Chinese and was frequently associated with the physical signs of bronchitis or bronchopneumonia. The head and backache were mild and in only one instance was the headache of the severity which often occurs in typhoid fever or in epidemic typhus.

Epistaxis and photophobia were occasional onset symptoms. Gastro-intestinal symptoms, aside from almost universal anorexia, were not striking; vomiting occurred in only 5 of the cases; in 3 of the Chinese, emesis ceased after roundworms were vomited. Mild diarrhea was present in 15% at the onset (Table 2).

Table 2.—Onset Symptoms

| Symptom | Chinese (%) | American (%) | Chinese and American (%) |
|---|---|---|---|
| Chill | 70 | 65 | 68 |
| Fever | 94 | 87 | 90 |
| Cough | 51 | 21 | 40 |
| Headache | 73 | 82 | 76 |
| Backache | 24 | 26 | 25 |
| Vomiting | 8 | 8 | 8 |
| Diarrhea | 10 | 21 | 15 |
| Epistaxis | 10 | 4 | 8 |
| Photophobia | 2 | 9 | 8 |
| Anorexia | 93 | 85 | 88 |

4. General Appearance of Patients. The most striking feature of the patient's general appearance was marked apathy. He felt sick and he appeared sick. He preferred to be undisturbed. He did not have the listless eye of the typhoid patient, rather the eyes were bright and alert like the "ferret-eye" of murine or epidemic typhus. This appearance differed from malaria in that the patient was sick all the time, not only during the paroxysms. His skin was often dry, ichthyotic and, in the more dehydrated cases, inelastic. He looked and felt weak, and was content to lie completely isolated from his environment and, unless urged, would disdain nourishment. Herpes simplex was noted only once.

Table 3.—Duration of Fever in 61 Cases

| Duration of fever (days) | No. of cases | | |
|---|---|---|---|
| | Chinese | American | Total |
| 10–15 | 6 | 11 | 17 |
| 16–20 | 19 | 10 | 29 |
| 21–25 | 10 | 1 | 11 |
| 26–30 | 2 | 1 | 3 |
| 31–35 | 0 | 0 | 0 |
| 36–40 | 1 | 0 | 1 |

5. Fever. The average duration of fever in 61 cases was 17.4 days, with the extremes 11 and 36 days. The average duration of fever in the Chinese patients was 18.3 days (11 to 36 days), in the Americans,

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16 days (10 to 26 days); 47% of the patients had a fever which lasted 16 to 20 days (Table 3).

The type of temperature curve which the patient manifested depended on the day of the disease on which he was admitted to the hospital. The curve as seen in patients who were admitted during the first few days of the disease or in those who first developed fever while in the hospital was either typhoidal, relapsing, remittent or intermittent. During the onset of the fever the temperature would rise gradually or abruptly (Charts 1 and 2) to a level of about 103° F. and either remain elevated (Chart 3) or fluctuate in a remittent or intermittent manner (Charts 2 and 4) for the next several days. Termination of fever occurred usually by cessation of the fluctuations but in some instances, particularly in the typhoidal type of curves, the course would terminate by lysis over a period of 3 to 6 days (Chart 5). A relapsing type of fever curve was also not infrequently seen. (Charts 4 and 6.)

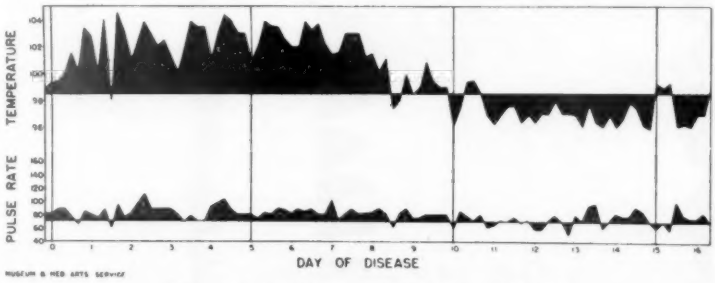


CHART 1.—Gradual onset of fever. Case 9.

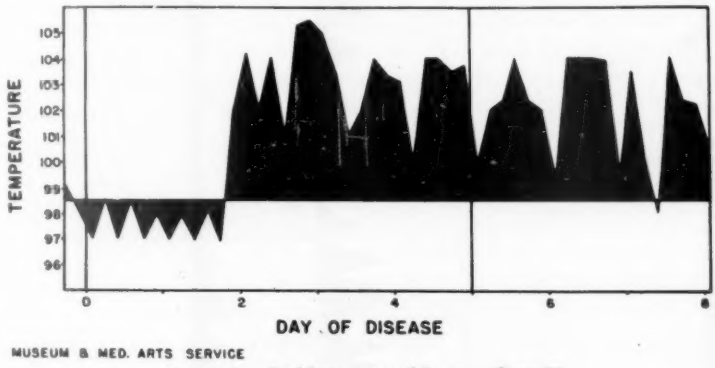


CHART 2.—Sudden onset of fever. Case 22.

The average temperature reading during the early course of the febrile period was 103° F.; on occasion, oral temperatures as high as 105° F. were recorded.

6. PULSE RATE. The average pulse rate in both the Chinese and American patients during the 1st week of the disease was elevated and averaged 102 per minute (80 to 120). This, according to Crozier-

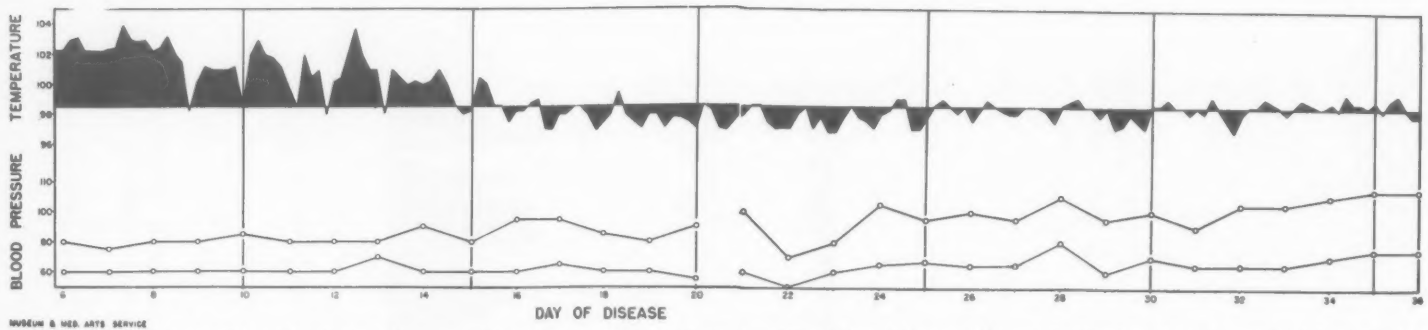


CHART 3.—Fever sustained for 4 days, then remittent for a period of 1 week. Chart also shows period of hypotension during course of fever and its disappearance during convalescence. Case 10.

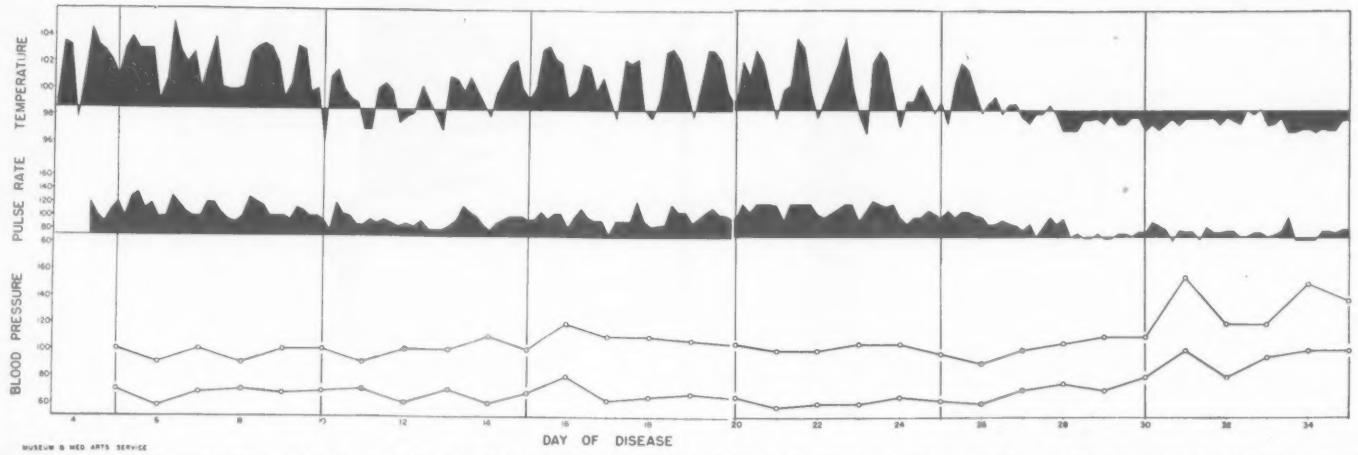


CHART 4.—Remittent type of fever curve in a patient who had a relapse of fever, a return of splenomegaly and the appearance of tender lymph nodes in the inguinal regions on the 12th day of the disease. The chart also shows hypotension during the two periods of fever with the return of blood pressure to the level presumably normal for him during convalescence. Case 12.

Griffith* chart of temperature and pulse relationship, would indicate a relative bradycardia. During the 2nd and 3rd weeks of the disease the pulse rate was frequently more rapid, averaging 120 (110 to 140) per minute at the peaks of the temperature rises. Though no abnormalities in pulse rhythm were noted, irregularities in the pulse rate were frequent and striking. Rates varying from 110 to 140 per minute during a ½ hour interval were noted on numerous occasions in several patients during the latter part of the febrile period.

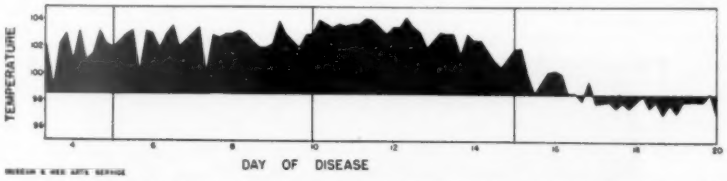


CHART 5.—Typhoidal type of fever curve with termination of fever by lysis. Case 49.

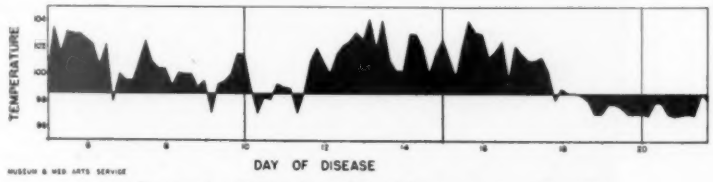


CHART 6.—Relapsing type of fever curve. Case 6.

7. BLOOD PRESSURE. In only 2 of 40 Chinese patients was the blood pressure normal from the onset of the disease throughout convalescence. In the others the blood pressure was low during the course of the febrile period and then gradually came up to normal during the period of convalescence. The fall in blood pressure applied to both systolic and diastolic levels, and when the return to normal occurred during convalescence there was no constancy in which returned first. The lowest point in the blood pressure curve was always reached at about the end of the 1st week of the disease (Charts 3 and 4). The average blood pressure reading on 35 cases early in the disease was 85/57 mm. Hg (100 to 70 systolic and 65 to 45 diastolic). When blood pressure finally returned to the level which seemed normal for the particular individual the average blood pressure reading was 120/77 (100 to 155 systolic and 70 to 100 diastolic). Return to normal occurred on the 31st day (21 to 49 days). Thus the blood pressure returned to normal after the fever subsided. Three cases of mild hypertension were observed in the series. One of these had an average blood pressure reading of 95/65 mm. Hg during the height of the disease; this gradually rose to an average of 140/95 during convalescence (Chart 4).

8. RASH AND CUTANEOUS MANIFESTATIONS. A typical rash (Fig. 4) or the remains of it was noted in 33 of 64 cases (51.5%). The inci-

* Crozier-Griffith temperature-pulse relationships; a pulse rate of 70 per minute for a temperature of 98.3°. An increase of 10 beats per minute for each rise of 1° F. in temperature.

nodes in the inguinal regions on the 12th day of the disease. The chart also shows hypotension during the two periods of fever with the return of blood pressure to the level presumably normal for him during convalescence. Case 12.

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dence of rash among the Chinese was 50% as compared to 54.1 for the Americans. The typical rash appeared early in the course of the disease, usually between the 3rd and 6th days and lasted 3 to 5 days. In most instances the rash was maculo-papular when it first appeared, less frequently it was macular. In no instance was the rash hemorrhagic or petechial in character nor did it give rise to any subjective discomfort. As the rash subsided the residue consisted of a faint mottling which took as long as a week to disappear. In full-blown cases the rash involved the face, trunk and extremities. No case of

FIG. 4.—Maculo-papular rash on trunk.

involvement of the palms or soles was seen. In some cases the rash was limited to the anterior and posterior chest, abdomen and upper arms. In a few cases, only the dorsum of the chest was involved.

9. SPLENOMEGALY. The spleen was palpable during the 1st week of the disease or on admission to the hospital in 88% of 40 Chinese. In 13% of the cases with splenomegaly, tenderness of the spleen was demonstrated on palpation. This tenderness disappeared on the 10th to 14th days of the disease, even though the spleen remained palpable for a longer time. The average day of the disease on which the

spleen was no longer palpable was the 28th (12 to 53 days). In 3 instances there was a recurrence of the splenomegaly; in 1 of these, an apparent relapse of the disease occurred (Chart 4). In the other 2 cases the spleen again became palpable when a relapse of tertian malaria occurred.

10. Lymphadenopathy. Regional lymphadenopathy was demonstrable in all but 4 of those patients in whom a primary eschar was present. In these exceptions the ulcer was located along the costal margins. Two Chinese patients presented enlargement and tenderness of inguinal nodes out of proportion to the enlargement of nodes elsewhere in the periphery; in neither of these cases was a primary lesion present. The inguinal adenopathy in the 2nd of these 2 cases occurred during an apparent relapse in the disease and was associated with a rise in temperature (Chart 4) and a recurrence of splenomegaly. One had to look with great care for enlargement of nodes in regions draining the site of the ulcers. In 4 instances they were found in unusual sites; the retro-sacral region, in the groove just internal to the head of the humerus, and on the lateral chest wall in the upper outer quadrant of the mammary area.

Generalized peripheral lymphadenopathy was demonstrated in 60 of 64 patients (93.7%). This lymphadenopathy developed early in the disease and was present in all cases during the 1st week of the disease at the time when regional adenopathy was also present. The general lymphadenopathy persisted for a longer time than did the regional. In 24 of the Chinese patients, no significant decrease in size of the nodes could be appreciated during the 2 to 4 months period of observation. In 16 of the cases the nodes appeared to decrease in size gradually during a period extending from the 40th to the 80th day of the disease, but in none of these did they become non-palpable.

11. Conjunctival Injection. An injection of the conjunctival blood-vessels was observed, on admission, in 34 of 64 cases (53%), the incidence in both the Chinese and Americans was the same. The injection of the conjunctival vessels disappeared during the 2nd, 3rd or 4th week of the disease; most of them at the end of the 2nd or beginning of the 3rd week. In 2 of the Chinese patients, inflammation of a purulent type was present and Koch-Weeks bacilli were obtained on culture. Two others developed a corneal ulcer on the 12th day of the disease.

12. Changes in the Eye-grounds. Rather characteristic changes in the eye-grounds were found in 30 of the 40 Chinese (75%) and in 14 of the 34 Americans (58%). These changes consisted of marked distention of the retinal veins, blurring of the disk margins, edema of the optic disks and retinæ, hemorrhages and the development of vitreous opacities. The engorgement of the retinal veins was almost a universal finding during the end of the 1st week or the beginning of the 2nd week of the disease. The veins were markedly engorged in the extreme cases, had irregular sausage dilatation and appeared compressed at the arteriovenous crossings. Subsequently edema of the disk and surrounding retina developed in 18 of the 40 Chinese. This

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edema varied in amount from less than 1 to 2 diopters. The edema was fairly diffuse usually, but occasionally was confined to the disk and was indistinguishable from a true papilledema such as is seen when intracranial pressure is increased. The cerebrospinal fluid pressure was normal in all except 1 of the patients with edema of the disks. That the swelling was not due to an optic neuritis was evidenced by the fact that visual acuity and visual fields were normal.

Four of the 18 patients who had edema of the disks developed retinal hemorrhages which were predominantly striate, but deep punctate hemorrhages were also seen along the general distribution of the veins.

"Cotton wool" exudates developed in 2 of the 18 patients who had edema of the disks. Fine vitreous opacities were seen in 7 out of the 40 patients, of which 3 had only venous engorgement as the other ocular change, while the remaining 4 had edema of the disks and retinæ. The appearance of edema of disks, retinal hemorrhages, "cotton wool" exudates and vitreous opacities occurred as early as the end of the 2nd week of the disease. They persisted long into convalescence and were among the last of the abnormal findings to disappear. A detailed report of the changes in the eye-grounds will be submitted by Capt. Harold G. Scheie.

13. Pulmonary Findings. Cough was a prominent symptom in 51% of the Chinese cases at the onset of the disease. Roentgen examination of the chest revealed the presence of pathologic changes in 24 of them. These consisted in the appearance of bronchitis with or without bronchopneumonia, bronchopneumonia, or enlargement of the hilar lymph nodes (Table 4). One patient had pleurisy complicating the pneumonic process. Pulmonary complications, occurring late in the disease, included pleural effusion (1 case), empyema (1 case), and lung abscess (1 case). These occurred in patients who had bronchopneumonia early in their course. The average duration of the febrile course in those patients who had acute pulmonary involvement was 2 to 4 days longer than in those who had no such complication (Table 4). One could not be certain whether the findings in the lungs which occurred early represented a complication or a part of the disease itself. The clinical and Roentgen evidence of bronchopneumonia and bronchitis disappeared during convalescence.

Table 4.—Pulmonary Findings in Chinese Patients Present on Admission

| Pulmonary lesion | No. of cases | Duration of fever (days) (average) |
|---|---|---|
| None | 16 | 18 |
| Enlargement of hilar nodes | 2 | 18 |
| Bronchitis | 9 | 20 |
| Bronchopneumonia | 9 | 20 |
| Bronchitis and bronchopneumonia | 4 | 22 |

14. Mental and Nervous System Manifestations. Symptoms referable to the mental and nervous system developed in 7 of the 40 Chinese cases and in 2 of the 24 American patients. These consisted of temporary psychosis, characterized by acute mania (1 case), disorientation and confusion (2 cases); coarse jerky movements of the eye-balls (1 case), purposeless twitchings of muscle groups of the

extremities (4 cases), paresthesias of hands and arms (1 case); generalized convulsions (2 cases); and meningismus (1 case). In all of these patients except 1, the spinal fluid cytology, serology and protein content were normal. The spinal fluid pressures were normal in all except 3 cases; in the 2 patients who had generalized convulsions they were low or zero. In the 3rd patient (Case 42) the spinal fluid pressures determined on the 14th and 17th days of the disease were elevated at 230 and 260 mm. of water and there was an increased number of cells (lymphocytes) as well as a trace of globulin present. There was no relationship between the presence or absence of azotemia and the presence of muscular twitchings, though the 2 patients who had generalized convulsions had the greatest degree of nitrogen retention. Except in 1 instance the nervous system manifestations all occurred after the 1st week of the disease, usually during the 2nd or 3rd week (Table 5). In the exception, a patient (Case 58) who developed a temporary psychosis, the mental symptoms occurred after the fever had subsided.

TABLE 5.—MENTAL AND NERVOUS SYSTEM MANIFESTATIONS

| Case No. | Duration of fever (days) | Mental or nervous manifestation | Day of disease disturbance noted | Duration of disturbance (days) | Spinal fluid | | | Azotemia | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Pressure in $H_2O$ | Cells | Globulin | Degree | Day of disease |
| 36 | 18 | Acute mania | 7 | 1 | 140 | 0 | 0 | 0 | |
| 58 | 18 | Disorientation, confusion, hallucinations, muscular twitching | 25 | 25 | .. | .. | .. | 0 | |
| 16 | 20 | Twitching of muscles of hands and arms | 10 | 3 | .. | .. | .. | 0 | |
| 13 | 26 | Coarse jerky movements of eyes | 22 | 10 | 140 | 0 | 0 | Plus 1 | 14–17 |
| 7 | 36 | Generalized rhythmic muscular twitchings | 14 | 11 | 135 | 0 | 0 | | |
| | | | | | 200 | 0 | 0 | Plus 1 | 16 |
| 3 | 19 | Convulsion generalized; disorientation, confusion, semistupor | 16 | 18 | 40 | 0 | 0 | Plus 3 | 16–24 |
| | | | 19 | .. | 0 | 0 | 0 | | |
| 8 | Died on 16 | 4 generalized convulsions, stupor | 16 | Died† | 0 | 0 | 0 | Plus 4 | 11–16 |
| 2 | 18 | Paresthesias and weakness of hands and arms | 14 | 7 | .. | .. | .. | 0 | |
| 42 | 17 | Meningismus, muscular twitchings | 14 | 11 | 230 | 60 | Trace | 0 | |
| | | | | | 260 | 26* | Trace | | |

* 97% lymphocytes.
† Died 4 hours after first convulsion.

15. HEPATOMEGALY. Hepatomegaly was not a common finding in this series of patients. Significant enlargement of the liver was found only in 2 American and in 1 Chinese patient. This finding was present on admission and disappeared during convalescence.

16. JAUNDICE. Mild jaundice was detected in 4 of the 40 Chinese patients, not any in the Americans. This occurred late in the febrile period or early in convalescence and persisted for 9 to 22 days. The direct Van den Bergh reaction in these cases was delayed, while the indirect or quantitative reaction revealed serum bilirubin values ranging from 0.3 to 1.3 mg. per 100 cc. (Table 6.)

17. DEAFNESS. Deafness was complained of by 11 of the 40 Chinese patients at some time during the course of the disease. In 8 of these,

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definite evidence of middle ear disease, sufficient to account for the impairment of hearing was found by Capt. Phillip A. Marden. In the remaining 3, the deafness was thought to be due to neural involvement. It was bilateral and was first complained of during the 3rd week of the disease, lasted for about 2 weeks and then disappeared. Two of these 3 patients had received quinine during the early course of the disease, hence some justifiable doubt may exist as to the exact cause of the deafness.

TABLE 6.—JAUNDICE

| Case No. | Duration of fever (days) | Day of disease on which icterus was first detected | Van den Bergh reaction | | | Duration of icterus (days) | Anemia |
|---|---|---|---|---|---|---|---|
| | | | Direct reaction | Indirect in mg./100 cc. serum | Day of disease | | |
| 3 | 19 | 24 | Delayed | 1.3 | 16 | 18 | Slight |
| | | | Delayed | 0.5 | 33 | | |
| | | | Delayed | 0.2 | 41 | | |
| 7 | 36 | 19 | Delayed | 0.4 | 21 | 22 | None |
| | | | Delayed | 0.4 | 32 | | |
| | | | Delayed | 0.2 | 41 | | |
| 19 | 21 | 17 | Delayed | 0.4 | 18 | 10 | Slight |
| | | | Delayed | 0.1 | 27 | | |
| 28 | 17 | 19 | Delayed | 0.3 | 20 | 18 | None |

18. STOMATITIS. Three of the 40 Chinese patients had a severe ulcerative stomatitis on admission, all of these were very seriously ill and 2 of them were semistuporous when admitted. One of the American patients (Case 42), who was semistuporous, developed a glossitis which disappeared during convalescence while vitamin concentrates were administered. Parotitis developed in 1 American patient (Case 49).

19. CARDIAC FINDINGS. The findings on auscultation of the heart in the 40 Chinese were not significant except for the presence of soft systolic basal murmurs, which were heard in 26 cases during the height of the illness. These disappeared during convalescence in all except 2. Electrocardiograms on 9 of the 40 patients revealed essentially normal tracings with the exception of evidence of left axis deviation in 2 (Table 7). These 2 patients also had evidence of increased heart size clinically and by Roentgen examination.

TABLE 7.—ELECTROCARDIOGRAPHIC FINDINGS

| Case No. | Duration of fever (days) | Day of disease on which EKG taken | Electrocardiogram interpretation |
|---|---|---|---|
| 2 | 18 | 27 | Normal |
| 3 | 19 | 10 | Left axis deviation |
| 5 | 24 | 15 | Normal |
| 7 | 36 | 15 | Normal |
| 8 | Died on 16 day | 11 | Normal |
| 10 | 16 | 6 | Normal |
| 12 | 24 | 4 | Normal |
| 14 | 14 | 8 | Normal |
| 33 | 23 | 20 | Left axis deviation |
| 42 | 17 | (See Table 9) | Myocardial damage |
| 46 | 10 | 11, 29, 43 | Normal |
| 61 | 13 | 38 | Normal |

In 2 of the American patients, basal systolic murmurs were heard. Another patient developed a transient pericardial friction rub on the 28th day of the disease, 19 days after fever had subsided; his blood urea nitrogen at this time was normal though it had been elevated slightly

during the fever. Electrocardiograms in 3 of this group of patients were made (Table 7). They were normal in 2, including the patient with the pericardial friction rub. In the 3rd patient findings suggestive of myocardial damage were obtained. This patient also had a gallop rhythm, and had evidence of partial heart block (Table 8).

TABLE 8.—ELECTROCARDIOGRAPHIC FINDINGS IN CASE 42, DURATION OF FEVER 17 DAYS

| Day of disease | Rate per min. | P-R interval (sec.) | Rhythm | P waves | QRS complexes | T waves |
|---|---|---|---|---|---|---|
| 14 | 150 | 0.16 | Sinus | Inverted in L-3 | Normal | Deeply notched in chest leads; rounded ST segments |
| 17 | 140 | 0.13 | Normal | Probably normal | Normal | Abnormal ST segment; flattening of T waves; notching in chest leads |
| 29 | 90 | 0.28 | Normal | Notched | Normal | Low and notched T-1 and Ter 3, 4, 5 |
| 44 | 95 | 0.17–0.19 | Normal | Inverted in L-3 | Normal | Normal; T-3 inverted; slight elevation: ST segment CR-3 |
| 83 | 100 | 0.17 | Normal | Normal P-3 inverted | Normal | Normal; T-3 inverted |

20. RELAPSE. Although some of the patients' temperature curves were of a relapsing type, only 1 patient in the series who had such a febrile curve also developed other evidences of a relapse. He was a Chinese with no primary eschar and was admitted on the 3rd day of his disease (Case 12). His fever curve was of the remittent type (Chart 4). The temperature fluctuations became less high, and on the 12th day his temperature had become almost normal. During this time his previously enlarged spleen gradually became smaller. On the 13th day the temperature again began rising though still remittent. The spleen again became large and also tender, and huge tender lymph nodes appeared in both inguinal regions. His temperature finally became normal on the 24th day of the disease. This patient's OXK titer did not become positive until the 21st day of the disease.

21. WEIL-FELIX REACTION (OXK). In 62% of the Chinese cases the Weil-Felix reaction first became positive at the end of the 2nd week of the disease, this being the time at which the temperature became normal in the average case. In the remainder of the patients the reaction became positive either at the end of the 1st week or after the beginning of the 3rd week (Table 9).

TABLE 9.—TIME AT WHICH WEIL-FELIX REACTION BECAME POSITIVE (PROTEUS OXK)

| End of week No. | No. of cases (%) |
|---|---|
| 1 | 8.1 |
| 2 | 62.2 |
| 3 | 10.8 |
| 4 | 10.8 |
| 5 | 2.7 |
| 6 | 5.4 |

The highest titer at which agglutination occurred varied in different patients from 1/25 to 1/6400 (the most frequent titer was 1/200) (Table 10). The highest titer in most instances was obtained about 2 weeks after cessation of fever. The average day of the disease on which the titer became negative was the 68th (42nd to 122nd) in

25 cases. In 11 others the reaction was still positive at the time of discharge on the 42, 47, 49, 70, 71, 85, 92, 98 and 100th day respecively (Table 10). Variation in titer in any one patient occurred from time to time, and smooth curves were not obtained (Charts 7, 8 and 9). This was probably due to the fact that the samples of blood

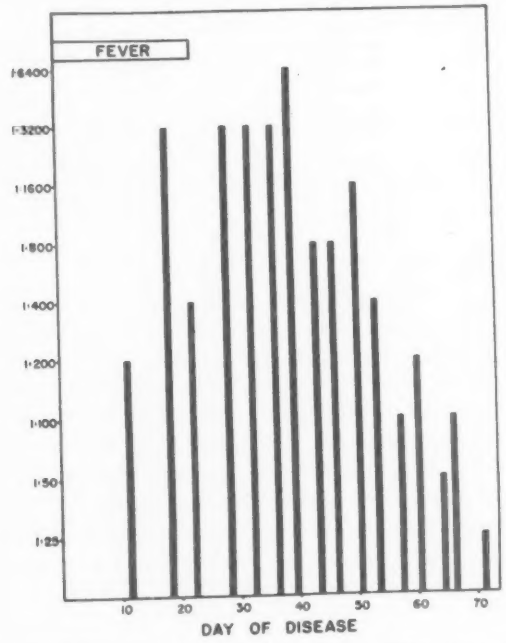


CHART 7.—High titer Weil-Felix reaction (proteus OXK) in a patient who had fever for 23 days. Case 30.

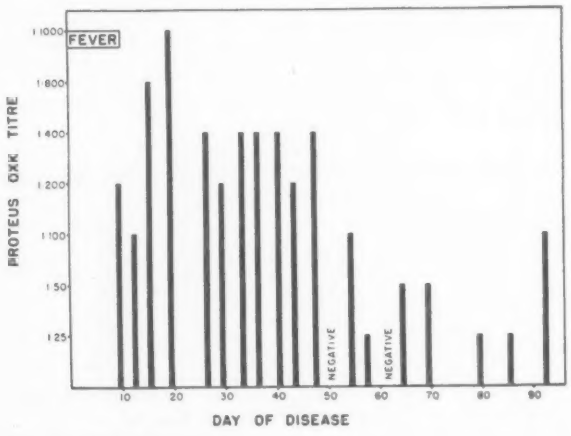


CHART 8.—Moderately high titer Weil-Felix reaction (proteus OXK) in a patient who had fever for 12 days. Case 21.

on any one patient were tested on different days and with different lots of antigen.

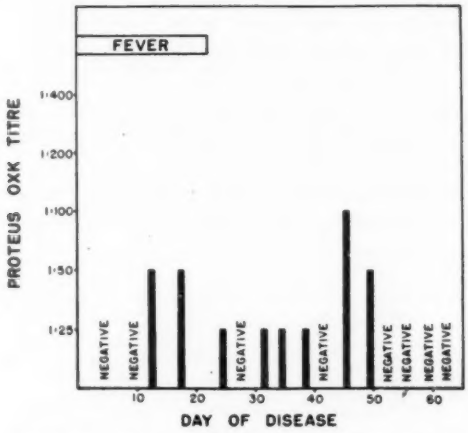


CHART 9.—Low titer Weil-Felix reaction (proteus OXK) in a patient who had fever for 22 days, a typical initial lesion, a typical rash, splenomegaly, regional and generalized lymphadenopathy and eye-ground changes. Case 31.

No significant correlation could be found between the clinical severity of the disease and the presence or absence of high titer in any single patient. The number of low, medium and high titer values was distributed about evenly in the group of patients in whom the fever lasted more than 18 days as compared to the group in which the course was shorter. However, the day of the disease on which the first positive titer was reached was on the average 7 days later in the group which had the more prolonged course of fever. The coincident existence of pneumonia did not appear to influence the titer. There was no significant difference between the length of time the titer remained positive in the group in whom the fever lasted more than 19 days as compared to the group in whom the fever lasted less (Table 10).

One factor which seemed to hold true in general was that those Chinese patients who had primary lesions had higher proteus OXK agglutination titers than the group without ulcers. In the former group, 15 of 24 patients had titers positive in a dilution greater than 1/200, while in the latter group only 1 patient had a titer in this range (Table 10).

The fact that the Americans had all been inoculated against ordinary typhus did not appear to influence either the dilution at which agglutination against proteus OXK occurred or the clinical severity of the disease.

22. PERIPHERAL BLOOD PICTURE. In the Chinese patients there was a moderate leukopenia during the 1st week of the disease, the average leukocyte count being 5500 per c.mm. in those patients who had no respiratory disease demonstrable. The mean neutrophilic percentage was 53, the lymphocytic 39, monocytic 7 and the eosinophilic 1 (Table 11). The leukopenia persisted until the end of the 4th week and then

gradually disappeared. The percentage of neutrophils gradually decreased as the lymphocytes increased, the latter reaching a maximum height at the end of the 3rd week. The percentage of monocytes remained practically at the same level throughout the period of observation. An interesting shift in the differential occurred after the 4th week of the disease (Chart 10). This was a rise in the percentage of eosinophils. The level rose from 1% during the febrile part of the disease to a level of 12 to 16 during the 6th to 12th weeks of observation. Hookworm infestation may have been responsible for the increase in total leukocyte count and the eosinophil percentage noted during convalescence. Hookworm ova were demonstrated in at least 33% of the patients.

TABLE 10.—RELATION OF PRESENCE OR ABSENCE OF PRIMARY ESCHAR TO HEIGHT OF PROTEUS OXK TITER

| Case No. | Duration of fever (days) | Day of disease on which titer first became positive | Degree of positive agglutination | Day of disease titer became negative | Complication |
|---|---|---|---|---|---|
| | | | *Eschar Present* | | |
| 1 | 24 | 43 | 1/400 | 85+ | Bronchopneum. |
| 2 | 18 | 15 | 1/200 | 85+ | Bronchitis |
| 8 | 16 (died) | 0 | 0 | .. | Convul. azotemia |
| 14 | 14 | 14 | 1/400 | 77 | Bronchopneum. |
| 15 | 24 | 22 | 1/400 | 63 | Bronchitis |
| 18 | 20 | 28 | 1/25 | 70 | Azotemia |
| 20 | 16 | 15 | 1/100 | 57 | Azotemia |
| 21 | 12 | 8 | 1/1600 | 92+ | |
| 22 | 20 | 15 | 1/1600 | 91 | Azotemia |
| 23 | 19 | 15 | 1/100 | | |
| 24 | 19 | 21 | 1/100 | 64 | Bronchopneum., otit. media |
| 25 | 26 | 28 | 1/200 | 71 | Bronchitis |
| 28 | 17 | 15 | 1/400 | 64 | Bronchopneum., jaundice |
| 29 | 15 | 15 | 1/200 | 100+ | Bronchopneum. |
| 30 | 23 | 14 | 1/6400 | 71+ | Bronchopneum., azotemia, anemia |
| 31 | 20 | 14 | 1/100 | .. | Bronchopneum. |
| 32 | 24 | 15 | 1/400 | 43 | |
| 33 | 23 | 15 | 1/1600 | 28 | Azotemia |
| 34 | 18 | 8 | 1/400 | 57 | Azotemia |
| 35 | 19 | 14 | 1/800 | 70+ | Bronchitis, azotemia |
| 36 | 18 | 14 | 1/200 | 42+ | |
| 37 | 16 | 14 | 1/1600 | 69 | Bronchopneum. |
| 38 | 16 | 14 | 1/800 | 57+ | Bronchitis, bronchopneum., azotemia |
| 39 | 16 | 7 | 1/800 | 42 | Bronchitis |
| 40 | 27 | 22 | 1/1600 | 47+ | |
| | | | *Eschar Absent* | | |
| 3 | 19 | 15 | 1/100 | 105 | Azotemia |
| 4 | 23 | 35 | 1/800 | 84 | Bronchitis |
| 5 | 24 | 29 | 1/200 | .. | Bronchopneum., pleurisy, azotemia |
| 6 | 18 | 15 | 1/50 | 56 | |
| 7 | 36 | 35 | 1/200 | 84 | Bronchopneum., azotemia |
| 9 | 11 | 15 | 1/200 | 56 | |
| 10 | 16 | 22 | 1/100 | 63 | |
| 11 | 21 | 43 | 1/25 | 49 | |
| 12 | 24 | 21 | 1/200 | 56 | Bronchopneum. |
| 13 | 26 | 29 | 1/100 | 112 | Bronchopneum., azotemia |
| 16 | 20 | 14 | 1/200 | 85 | Bronchitis |
| 17 | 18 | 29 | 1/50 | 57 | Bronchopneum. |
| 19 | 21 | 15 | 1/200 | 92 | Jaundice |
| 26 | 12 | 15 | 1/200 | 63 | Bronchopneum. |
| 27 | 14 | 15 | 1/50 | | |

The trends in the white formed elements of the peripheral blood in those patients who also had bronchopneumonia were rather similar to those described; but the initial leukopenia was slightly less (Chart 11).

A slight degree of anemia developed in the Chinese patients, the average hemoglobin decreasing from 14 to 12 gm. during the first 3 weeks of the disease. The anemia disappeared during convalescence.

TABLE 11.—FORMED ELEMENTS OF PERIPHERAL BLOOD IN UNCOMPLICATED CASES (CHINESE)

| Week of disease | Average leukocyte count | Differential (%) | | | | Hb. (gm.) | No. of Cases |
|---|---|---|---|---|---|---|---|
| | | Neut. | Lymphs. | Mono. | Eosin. | | |
| 1 . . | 5500 | 53 | 39 | 7 | 1 | 14 | 9 |
| | (3400–7850) | (39–62) | (21–55) | (1–17) | (0–2) | (10.4–17.5) | |
| 2 . . | 6750 | 46 | 48 | 5 | 1 | 13 | 10 |
| | (3900–10,800) | (23–77) | (21–72) | (0–12) | (0–4) | (11.4–16.0) | |
| 3 . . | 6150 | 37 | 55 | 6 | 2 | 12 | 12 |
| | (4600–8800) | (11–55) | (42–85) | (2–12) | (0–6) | (9.4–13.8) | |
| 4 . . | 6330 | 44 | 48 | 6 | 2 | 13 | 12 |
| | (3300–8400) | (30–58) | (39–65) | (0–21) | (0–6) | (10.4–14.5) | |
| 5 . . | 7626 | 44 | 40 | 8 | 8 | 12 | 12 |
| | (3700–17,200) | (26–61) | (31–53) | (0–16) | (0–29) | (9.5–14.2) | |
| 6 . . | 7725 | 46 | 33 | 5 | 16 | 12 | 11 |
| | (4200–14,400) | (33–58) | (24–45) | (0–10) | (2–36) | (10.4–15.2) | |
| 7 . . | 8372 | 39 | 40 | 8 | 13 | 13 | 11 |
| | (4400–13,600) | (32–49) | (28–52) | (1–12) | (2–26) | (7.6–14.4) | |
| 8 . . | 9441 | 40 | 38 | 6 | 16 | 12 | 12 |
| | (5500–15,400) | (23–53) | (23–48) | (2–15) | (1–34) | (10.2–13.9) | |
| 9 . . | 9350 | 44 | 38 | 6 | 12 | 13 | 11 |
| | (6300–12,400) | (22–54) | (25–56) | (2–9) | (5–17) | (10.6–14.0) | |
| 10 . . | 8506 | 44 | 35 | 6 | 15 | 14 | 8 |
| | (3450–13,200) | (21–58) | (30–43) | (2–9) | (3–42) | (11.0–15.0) | |
| 11 . . | 8521 | 47 | 34 | 5 | 14 | 13 | 7 |
| | (6150–10,850) | (27–60) | (24–44) | (1–10) | (1–43) | (11.0–14.0) | |
| 12 . . | 8125 | 48 | 35 | 5 | 12 | 13 | 6 |
| | (6700–12,450) | (34–64) | (20–56) | (2–8) | (1–28) | (11.4–14.2) | |

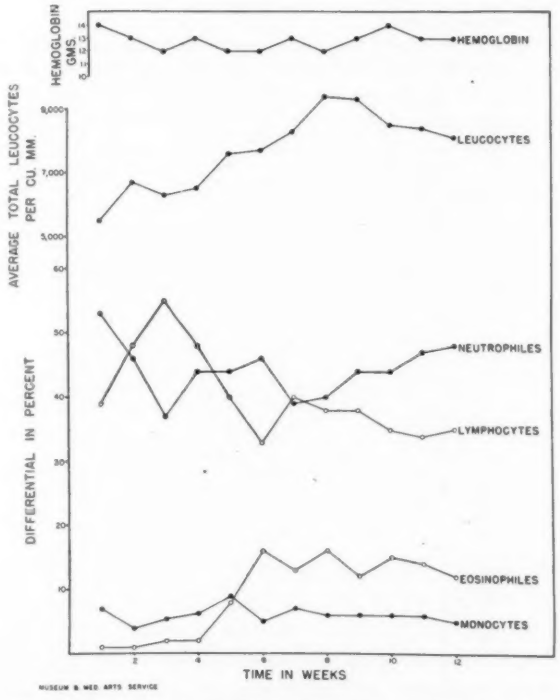


CHART 10.—Trends in the average total leukocyte count, differential and hemoglobin in Chinese patients having no evidence of pulmonary involvement. Note eosinophilia late in convalescence.

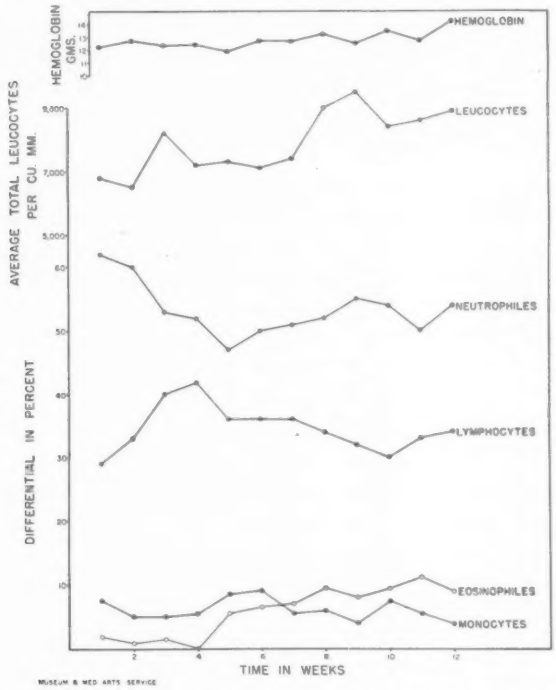


CHART 11.—Trends in average total leukocyte count, differential and hemoglobin in Chinese patients who had Roentgen evidence of bronchopneumonia.

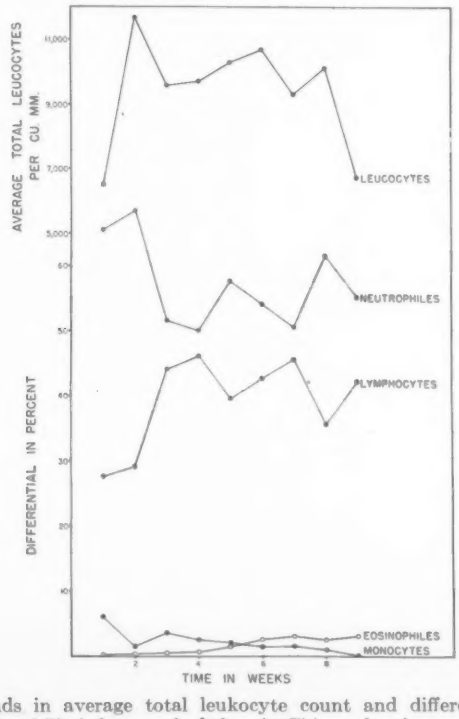


CHART 12.—Trends in average total leukocyte count and differential in American patients. Eosinophilia is less marked than in Chinese but is nevertheless definite.

In the American patients a leukopenia was present during the 1st week of the disease; however subsequently a mild leukocytosis developed and this persisted until the end of the 8th week. The trends in the differential and in the hemoglobin were similar to those in the Chinese (Chart 12, Table 12).

TABLE 12.—FORMED ELEMENTS OF PERIPHERAL BLOOD IN UNCOMPLICATED CASES (AMERICAN)

| Week of disease | Average leukocyte count | Differential (%) | | | | Hb. (gm.) | No. of cases |
|---|---|---|---|---|---|---|---|
| | | Neut. | Lymphs. | Mono. | Eosin. | | |
| 1 | 6,545 (3800–8800) | 65.4 (50–79) | 27.2 (17–42) | 6.0 (0–15) | 0.1 (0–2) | 16.1 (12.5–17.5) | 10 |
| 2 | 11,750 (8700–18,350) | 68.6 (51–87) | 29.0 (12–45) | 1.7 (0–11) | 0.4 (0–2) | 15.0 (11.5–18.0) | 18 |
| 3 | 9,700 (5800–19,000) | 51.5 (34–76) | 44.4 (24–62) | 3.2 (0–12) | 0.6 (0–3) | 15.0 (12.0–18.0) | 19 |
| 4 | 9,760 (5600–16,550) | 50.1 (26–72) | 45.9 (27–70) | 2.1 (0–14) | 0.8 (0–5) | 14.5 (13.5–15.0) | 16 |
| 5 | 10,390 (6500–15,450) | 57.1 (45–71) | 39.6 (23–51) | 2.0 (0–6) | 1.3 (0–2) | 14.2 (12.5–15.0) | 10 |
| 6 | 10,745 (7400–15,950) | 54.1 (40–68) | 42.3 (30–55) | 1.1 (0–3) | 2.5 (0–10) | 14.0 (12.5–15.0) | 10 |
| 7 | 9,300 (6850–12,400) | 50.5 (35–77) | 45.5 (19–58) | 1.1 (0–5) | 3.0 (0–12) | 13.2 (12.5–14.0) | 8 |
| 8 | 10,110 (7500–12,600) | 61.2 (52–72) | 35.2 (26–45) | 0.8 (0–2) | 2.6 (0–9) | 12.5 (12.0–13.0) | 5 |
| 9 | 6,780 (6200–11,050) | 55.0 (43–67) | 42.4 (31–57) | 0 .. | 3.0 (0–7) | 14.5 (14.0–15.5) | 5 |

TABLE 13.—VALUES FOR BLOOD UREA NITROGEN IN PATIENTS WITH AZOTEMIA

| Case No. | Day of disease admitted | Duration of fever (days) | B.U.N. (mg. per 100 cc.) (days of disease in parentheses) | Abnormal urinary findings |
|---|---|---|---|---|
| 3 | 7 | 19 | 63, 52, 24, 16, 8 (16, 20, 24, 26, 35) | + |
| 5 | 7 | 24 | 20, 25, 25, 18, 11 (14, 16, 20, 24, 27) | + |
| 7 | 9 | 36 | 17, 23, 15, 8 (14, 16, 15, 24) | + |
| 8 | 8 | Died on 16th day | 28, 50, 108 (11, 12, 16) | + |
| 13 | 11 | 26 | 23, 30, 30, 31, 13 (11, 14, 18, 21, 24) | + |
| 18 | 15 | 20 | 32, 16, 14 (20, 29, 40) | + |
| 20 | 6 | 16 | 25, 10 (9, 17) | + |
| 22 | Onset in hospital | 20 | 71, 45, 13 (11, 16, 23) | + |
| 30 | 9 | 23 | 25, 26, 8 (12, 15, 23) | 0 |
| 33 | 7 | 23 | 17, 26, 40, 38, 15 (8, 12, 16, 19, 23) | + |
| 34 | 5 | 18 | 20, 28, 25, 12 (6, 9, 13, 16) | + |
| 37 | 12 | 19 | 21, 13, 8 (13, 18, 21) | + |
| 38 | 7 | 16 | 18, 27, 12 (8, 11, 15) | + |
| 41 | 8 | 26 | 34, 18 (13, 23) | + |
| 42 | 8 | 17 | 13, 22, 25, 30, 9 (11, 15, 16, 21, 29) | 0 |
| 46 | 7 | 10 | 32, 15, 11 (9, 11, 19) | 0 |

23. AZOTEMIA. Of the 40 Chinese patients, 13 manifested a mild to a moderate azotemia during the course of the fever (Table 13). This occurred during the 2nd and 3rd weeks of the disease and particularly in those patients in whom the fever was prolonged or in those in whom the illness was more intense. The azotemia bore no relationship to the presence or absence of bronchopneumonia.

Three of the Americans developed azotemia. This was most marked

in the patient (Case 42) who was semistuporous and had an increased cerebrospinal fluid pressure.

24. Urinary Findings. Abnormal findings in the urine* were detected in 19 of the Chinese and in 6 of the American patients. These occurred irrespective of azotemia but occurred in all except 3 of the patients who had azotemia. These findings consisted of albumin, coarse or fine granular and hyaline casts, leukocytes and occasionally R.B.C. (Table 14). Casts and albuminuria were the most constant findings in these cases. Their appearance was transient and occurred especially during the 2nd and 3rd weeks of the disease.

Table 14.—Urinary Findings

| Case No. | Duration of fever (days) | Day of disease urinary abnormality found | Albuminuria | Casts per low power field | Leukocytes per high power field | R.B.C. per high power field | Degree of azotemia |
|---|---|---|---|---|---|---|---|
| 1 | 24 | 29 | Plus 1 | 0 | Many | 0 | 0 |
| 2 | 18 | 11 | Trace | 10–15 coarse gran. | 0 | 0 | |
| | | 14 | Trace | 1 coarse gran. | Occ. | 0 | 0 |
| | | 17 | Plus 1 | 2–3 coarse gran. | 0 | 0 | |
| 3 | 19 | 9 | Plus 1 | 1–2 coarse gran. | 0 | 0 | |
| | | 12 | Plus 2 | 1–2 hyaline; 1–2 granular | Occ. | 0 | Plus 3 |
| | | 15 | Plus 1 | Many coarse gran. | 0 | 0 | |
| 5 | 24 | 14 | Plus 2 | 1–3 granular | 0 | Occ. | |
| | | 16 | Plus 4 | Mod. hyaline, many coarse gran. | Occ. | 20–40 | Plus 1 |
| 6 | 18 | 11 | Plus 1 | Numerous hyaline, occ. red blood cell cast | 10–15 | 1–2 | 0 |
| 8 | Died 16th day | 10 | Plus 1 | 4 granular moderate | Occ. | 0 | Plus 4 |
| | | 12 | Plus 2 | Coarse granular | 0 | 0 | |
| 10 | 16 | 6 | Plus 1 | Mod. coarse gran. | 0 | 0 | 0 |
| 12 | 24 | 5 | Plus 2 | 1–2 waxy rare gran. | 5–10 | 1–2 | Plus 2 |
| 13 | 26 | 12 | Plus 1 | 2 coarse granular | 3–6 | 0 | Plus 1 |
| 19 | 21 | 14 | Trace | 1–2 granular | Occ. | 0 | 0 |
| 20 | 16 | 21 | Trace | Occ. hyaline | 0 | 0 | Plus 1 |
| 22 | 20 | 8 | 0 | 2–3 granular | 0 | 0 | Plus 4 |
| | | 14 | Trace | 2–4 granular | 0 | 0 | |
| 28 | 17 | 11 | Plus 1 | 10–15 granular | Occ. | 0 | 0 |
| 32 | 24 | 17 | 0 | 5 granular | 3–4 | 0 | 0 |
| 33 | 23 | 7 | Plus 1 | 6–8 fine granular | 0 | 0 | Plus 3 |
| | | 9 | Trace | Few granular | 0 | 0 | |
| | | 16 | Plus 2 | 15–20 granular | 3–5 | 0 | |
| 34 | 18 | 6 | 0 | 2 granular | 3–4 | 0 | Plus 1 |
| | | 13 | Plus 1 | 12–15 granular, few hyaline | 0 | 0 | |
| 35 | 19 | 13 | 0 | 4–5 granular | 3–4 | 0 | Plus 1 |
| | | 18 | Plus 2 | 15–20 coarse gran. | 2–4 | 0 | |
| 37 | 16 | 9 | Plus 2 | 2–3 granular | 6–8 | 0 | 0 |
| 38 | 16 | 8 | Plus 2 | 12–15 granular | 3–5 | 0 | Plus 1 |
| 41 | 26 | 9 | Plus 2 | Many hyaline, many fine granular | 0 | 0 | Plus 2 |
| 50 | 19 | 8 | Plus 2 | 2–3 granular | 0 | 0 | 0 |
| | | 12 | 0 | Occ. fine granular | | | |
| 51 | 24 | 11 | Plus 1 | Occ. fine granular | 0 | 0 | |
| | | 13 | Trace | 6–8 granular | 0 | 0 | 0 |
| | | 27 | 0 | Few granular | 0 | Occ. | |
| 54 | 12 | 7 | Trace | Occ. hyaline | 0 | 0 | |
| | | 18 | 0 | 3 granular | 3–5 | 0 | 0 |
| 55 | 14 | 6 | Trace | Occ. coarse granular | 5–16 | 1–2 | 0 |
| 57 | 18 | 7 | 0 | 1–2 fine hyaline | Occ. | 0 | |
| | | 12 | Plus 1 | 8–10 fine hyaline | Occ. | 0 | 0 |

25. Comparison of the More Common Clinical Findings and OXK Titer in Patients With and Without Primary Ulcer. With the single exception of the OXK titer already commented on,

* A number of samples of urine were checked by Capt. C. F. Kay of the Cardio-renal Section.

the patients with primary ulcers did not show important difference when compared to the group without ulcers. The incidence of rash, splenomegaly, lymphadenopathy and eye-ground changes as well as the duration of fever was approximately the same in both groups (Tables 15 and 16).

TABLE 15.—CLINICAL FINDINGS AND OXK TITER IN CHINESE PATIENTS WITH PRIMARY ULCER

| Case No. | Day of disease admitted | Duration of fever (days) | Spleno-megaly | Generalized lymph-adenopathy | Eye-ground changes | Rash | Highest OXK titer |
|---|---|---|---|---|---|---|---|
| 1 | 11 | 24 | + | + | + | + | 1/400 |
| 2 | 8 | 18 | + | + | + | − | 1/200 |
| 8 | 8 | Died on 16th day | + | + | 0 | + | Not pos. |
| 14 | 9 | 14 | + | + | + | + | 1/400 |
| 15 | 8 | 24 | + | + | + | − | 1/400 |
| 18 | 15 | 20 | + | + | + | − | 1/25 |
| 20 | 6 | 16 | + | + | + | − | 1/100 |
| 21 | 5 | 12 | 0 | + | 0 | − | 1/1600 |
| 22 | −4 | 20 | + | + | + | 0 | 1/1600 |
| 23 | 10 | 19 | + | + | 0 | − | 1/100 |
| 24 | 9 | 19 | + | + | 0 | − | 1/100 |
| 25 | 16 | 26 | + | + | 0 | − | 1/200 |
| 28 | 9 | 17 | + | + | + | − | 1/400 |
| 29 | 8 | 15 | + | + | + | + | 1/200 |
| 30 | 9 | 23 | + | + | + | − | 1/6400 |
| 31 | 4 | 20 | + | + | + | + | 1/100 |
| 32 | 4 | 24 | + | 0 | 0 | + | 1/400 |
| 33 | 7 | 23 | + | + | + | + | 1/1600 |
| 34 | 5 | 18 | + | + | 0 | + | 1/400 |
| 35 | 12 | 19 | + | + | + | − | 1/800 |
| 36 | 6 | 18 | + | + | + | + | 1/200 |
| 37 | 8 | 16 | + | + | + | + | 1/1600 |
| 38 | 7 | 16 | + | + | + | + | 1/800 |
| 39 | 4 | 16 | + | + | + | − | 1/800 |
| 40 | 12 | 27 | + | + | 0 | − | 1/1600 |

+ means present. 0 means none present. − means not present while in ward.

TABLE 16.—CLINICAL FINDINGS AND OXK TITER IN CHINESE PATIENTS WITHOUT PRIMARY ULCER

| Case No. | Day of disease admitted | Duration of fever (days) | Spleno-megaly | Generalized lymph-adenopathy | Eye-ground changes | Rash | Highest OXK titer |
|---|---|---|---|---|---|---|---|
| 3 | 7 | 19 | + | + | 0 | + | 1/100 |
| 4 | 9 | 23 | + | + | + | − | 1/800 |
| 5 | 7 | 24 | + | + | + | − | 1/200 |
| 6 | 4 | 18 | + | + | + | − | 1/50 |
| 7 | 9 | 36 | + | + | + | + | 1/200 |
| 9 | −4 | 11 | + | + | + | + | 1/200 |
| 10 | 5 | 16 | + | + | + | + | 1/100 |
| 11 | 10 | 21 | + | + | + | − | 1/25 |
| 12 | 3 | 24 | + | + | + | + | 1/200 |
| 13 | 11 | 26 | 0 | 0 | + | + | 1/100 |
| 16 | 2 | 20 | + | + | 0 | + | 1/200 |
| 17 | 5 | 18 | 0 | + | + | − | 1/50 |
| 19 | 6 | 21 | + | + | + | − | 1/200 |
| 26 | 7 | 12 | 0 | + | + | − | 1/200 |
| 27 | 7 | 14 | + | + | 0 | − | 1/50 |

+ means present. 0 means absent. − means not present while in ward.

26. MORTALITY. In this series of 64 patients, only 1 death occurred. This patient was a Chinese (Case 8) who appeared to be doing well except for a rapidly rising blood urea nitrogen. On the 16th day of his disease he developed a generalized convulsion, became comatose, and went into shock. Lumbar puncture revealed a cerebrospinal fluid pressure of zero. Despite intensive measures directed against shock the patient died 3 hours later after 3 more generalized convulsions.

27. TREATMENT. The treatment employed in this series of patients was essentially symptomatic and supportive.

General measures included complete bed rest and an adequate intake of fluid and calories in readily assimilable form. Fluid was supplied by vein only if the patient could not take it by mouth. Each patient received in addition 2 brewer's yeast tablets, 7 gr. of sodium chloride and 25 mg. of ascorbic acid 3 times each day. Supplements of sweetened diluted canned milk were given to the Chinese patients between meals.

Other therapy included oxygen inhalation if cyanosis was present, blood transfusion if in shock, and adequate sedation when indicated. We believe death in 1 patient with an increased cerebrospinal fluid pressure may have been prevented by spinal drainage.

Sulfadiazine was administered to 10 patients with and without bronchopneumonia without detectable benefit. The dosage employed was 4 gm. as an initial dose and 2 gm. every 4th hour for 4 to 5 days. Neoarsphenamine (0.6 gm.) was administered to 2 patients early in the course of the disease without noticeable benefit. Convalescent blood, with a high titer (1/3200) against proteus OXK antigen was administered 5 days after onset of the fever to 2 patients but did not appear to influence the course of the disease in the amounts given (500 cc.). Many of the patients had had quinine or atabrine prior to and even after admission to the hospital without detectable effect on the course of the disease.

Since some of the patients had the primary lesions on the skin excised for biopsy and other studies, it was thought worth-while to compare the course of the disease in this group with that in which the ulcer was allowed to remain in order to see whether or not the excision of the primary focus shortened the subsequent course. It did not. The average duration of the fever was longer in the group that had the ulcer excised.

**Summary.** Clinical and laboratory data are presented on a series of 24 American and 40 Chinese patients who had a disease which appeared to be identical with tsutsugamushi or Japanese river fever, also called mite or "scrub" typhus. These data include observations on the temperature, pulse, blood pressure, rash, primary eschar, eye-grounds, and on the incidence and duration of splenomegaly and regional and generalized lymphadenopathy. Severe pulmonary, cerebral and cardiac symptoms are described as well as other complications. The laboratory data include the results of periodic total and differential white blood cell counts, hemoglobin and blood urea nitrogen determinations and urinalyses. The nature and duration of positive Weil-Felix reaction (proteus OXK) are described and a difference between the OXK titer in patients with and without primary ulcers is pointed out. Early in the disease, interesting eye-ground changes were observed, these persisted into convalescence. Azotemia was noted during the 2nd or 3rd weeks of fever. One of the patients in the series appeared to undergo a true relapse. The mortality in the series was 1.5%.

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## ON THE TOXICITY OF STREPTOTHRICIN

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Statements on the toxicity of streptothricin[6] have been published by Robinson and his co-workers. Thus Robinson[4] working with material of low potency (5 to 50 units per mg.) showed that the 5 unit material was of very low toxicity on a weight basis and 5 gm. (25,000 units) per kilo produced no evidence of toxicity when administered intravenously. However, the more potent material (by this is presumably meant the 50 unit material) was toxic intravenously at 50 mg. (2500 units) per 20 gm. mouse or 125,000 units per kilo. Some evidence of toxicity occurred at 50,000 units per kilo but no deaths. There appeared to be a relation between toxicity and rate of injection. At doses approaching the lethal dose mice collapsed with apparent respiratory failure and would appear dead. Respiration would finally recommence and return to normal within an hour. Intraperitoneally 60 mg. per mouse (150,000 units per kg.) produced toxic signs in 10 to 15 minutes that might persist for 24 hours, although the mouse eventually recovered. In these studies all observed deaths took place within 24 hours.

In a later paper[3] Robinson and his co-workers used aqueous solutions of material varying in potency from 5 to 300 units per mg. Mice (CFI albinos 18 to 21 gm.) were treated by various routes with a single dose and then observed for 5 days. When administered intravenously 60,000 units per kg. produced some deaths, but there was no effect by oral or subcutaneous routes. However, the authors' published figures show that the $L_D50$ (dose lethal for 50% of animals) by the intravenous and subcutaneous routes was almost identical (between 185,000 and 200,000 units per kilo). Orally 250,000 units per kg. were tolerated without effect but at 500,000 units per kg. anorexia and loss of weight developed and 10% of the mice died. In a still later paper[5] these same authors tested the toxicity of streptothricin by the sub-

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cutaneous route. The $L_D50$ obtained was approximately 3100 units per 20 gm. mouse or 155,000 units per kg. Deaths occurred on the 6th, 7th and 9th days.

**Technique.** In this work, Swiss mice weighing 19 to 21 gm. were used. Most inoculations were by the intravenous route using 0.5 ml. volume, but some groups received material subcutaneously, intramuscularly, intraperitoneally or by mouth. All animals which survived were observed for at least 21 days. Autopsies were performed on all those which died, except those dying during the night (when postmortem changes might influence the results). Portions of liver, spleen, pancreas, adrenal, kidney, voluntary muscle, heart, duodenum, jejunum, ileum, colon, cerebrum, cerebellum and medulla, and after subcutaneous inoculation, the site of infection, were taken for microscopic examination. They were fixed in Zenker acetic fluid and stained with eosin-methylene blue. Kidneys and some other tissues were also stained with Weigert's fibrin stain.

**Material.** The streptothricin to be tested varied in potency from 84.5 to 529 units per mg. The latter material represents a highly purified product regenerated from a crystalline derivative.[2] In addition, one fraction, obtained during the purification process but without any antibiotic activity, was tested. The unit of activity is not an absolute but rather a reference unit and corresponds to the unit of Foster and Woodruff.[1] Activity of a given preparation has been ascertained by comparison with a standard, tested at the same time and under the same conditions, which standard had a given value in reference units. This value in reference units had been obtained by comparison with a sample of streptothricin of given potency in reference units kindly supplied by Dr. J. W. Foster of Merck & Co., Inc.

**Results.** In most cases only small quantities of material were available and only few mice at one or two concentrations could be tested. It soon became apparent that following intravenous inoculation two types of toxic reaction occurred. The first was apparent immediately following or even during inoculation. The mice would run for a few steps and then collapse. Breathing became very labored and then ceased. In some cases the mice died and in others they recovered completely within a few minutes. The second type of reaction began to appear about 24 hours after inoculation or might be more delayed. The mice became listless, anorexic, and the fur was ruffled. Breathing was labored, and the animals often sat back on their hind legs for long periods and showed a tendency to fall backwards. Death followed quietly, although on rare occasions there were convulsions, occurring anywhere from the 2nd to the 12th day after inoculation, and from 1 to several days after the animals became sick. Most of the deaths occurred before the 8th day and 22% on the 6th day. If a record was kept of the amount of food eaten by the mice for each 24 hour period, the consumption was found to decrease markedly during the 2nd day in the mice receiving the largest doses. In those receiving doses small enough to cause few if any deaths, this decrease in consumption occurs on the 5th day. This anorexia seems to be a prime symptom and often precedes the appearance of any other marked malaise.

When these two types of toxic reaction were examined in relation to the type of material used in the toxicity experiments, certain points were noted. Thus the mortality rate of delayed deaths is related to

the number of units of streptothricin inoculated and not to the purity or any other characteristics of a given batch of material. It would seem, therefore, to be due to the streptothricin. On the other hand, the rate of acute deaths bears little relation to the number of units of streptothricin inoculated (Table 1). It does, however, bear a definite relation to the purity of a given batch of material. Thus (Table 2) the least pure sample tested—ST1121 84.5 units per mg.—killed immediately all mice receiving doses of 375, 458 and 1146 units intravenously while the purest preparation of streptothricin killed immediately only 1 mouse of 4 receiving 2630 units intravenously and none of those receiving 2296 units, 1766, 1322 and so on down to 88 units. It is clear from this that acute deaths can be produced with highly purified material, but only with very large doses intravenously (132,480 units per kg.). From these results it would seem that, for the most part, the acute deaths were due to impurity other than streptothricin. The nature of the acute deaths resembles closely those produced by histamine and related substances.

TABLE 1.—COMBINED INTRAVENOUS TOXICITIES OF ALL SAMPLES OF STREPTOTHRICIN TESTED

| Dosage (units) | Immediate toxicity | | Delayed toxicity | |
|---|---|---|---|---|
| | No. of mice | Mortality (%) | No. of mice | Mortality (%) |
| 3000–4140 | 6 | 100.0 | | |
| 2500–3000 | 41 | 56.1 | 18 | 88.9 |
| 2000–2500 | 35 | 25.7 | 26 | 92.3 |
| 1500–2000 | 37 | 27.0 | 27 | 85.2 |
| 1000–1500 | 45 | 17.8 | 20 | 89.2 |
| 88–1000 | 77 | 20.8 | 61 | 50.8 |

The mice observed for delayed toxicity represent, of course, those surviving the immediate reaction.

The detailed results on 4 materials, of which sufficient was available to test in a moderate number of mice, are shown in Table 2. It is seen that the amount in units required to kill immediately decreases with decreasing potency (and purity). Thus the approximate immediate $L_D50$ for S326–3273 (pure streptothricin) is >2630 units, for 95K (330 units per mg.) is 2400 units, for 125K (250 units per mg.) is 1728 units, and for ST1121 (84.5 units per mg.) only 286 units. On the other hand, the $L_D50$ for delayed deaths occurs at more nearly the same level for the purest material and for the least pure. Streptothricin, or at least the impure material, is also toxic by routes of administration other than intravenous. However, the delayed toxicity is considerably less by these other routes (stomach tube, subcutaneous, intramuscular and intraperitoneal injection), and no immediate deaths, or indeed any reactions, occur after administration by these routes (Table 2).

**Pathologic Changes.** That the material, when given intravenously, has a marked effect on the blood-vessels can be observed even in the living animal. Thus, even after the administration of purified material, in most of those mice which survive for 24 hours or longer marked gangrene of the tail develops distal to the point of intravenous inocula-

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tion and this part of the tail is eventually lost. In addition, hemorrhages may occur in the skin and are particularly noticeable in the ears. Following subcutaneous inoculation, inflammation occurs at the site of injection.

TABLE 2.—TOXICITY OF SAMPLES OF STREPTOTHRICIN OF VARYING POTENCY

| Route of inoculation | Dosage (units per mouse) | Immediate deaths | Delayed deaths |
|---|---|---|---|
| ST1121—84.5 units per mg. | | | |
| IV | 1146 | 4/4 | |
| | 458 | 5/5 | |
| | 375 | 5/5 | |
| | 286 | 5/10* | 2/5 |
| | 228 | 0/10 | 4/10 |
| 95K—330 units per mg. | | | |
| IV | 4106 | 3/3 | |
| | 2933 | 9/10 | 1/1 |
| | 2567 | 8/10 | 2/2 |
| | 2281 | 4/10 | 6/6 |
| | 2053 | 0/10 | 10/10 |
| OS | 1027 | 0/18 | 5/18 |
| IM | 977 | 0/20 | 2/20 |
| 125K—250 units per mg. | | | |
| IV | 1997 | 3/3 | |
| | 1810 | 5/10 | 4/5 |
| | 1498 | 2/9 | 5/7 |
| | 998 | 1/6 | 5/5 |
| | 499 | 0/1 | 1/1 |
| IP | 1810 | 0/8 | 1/8 |
| S326-3273—529 units per mg. | | | |
| IV | 2630 | 1/4 | 3/3 |
| | 2296 | 0/1 | 1/1 |
| | 1766 | 0/4 | 4/4 |
| | 1322 | 0/4 | 4/4 |
| | 882 | 0/4 | 2/4 |
| | 661 | 0/4 | 2/4 |
| | 441 | 0/4 | 1/4 |
| | 220 | 0/4 | 1/4 |
| | 88 | 0/4 | 0/4 |
| STCP—102 units per mg. | | | |
| SC | 4500 | 0/6 | 5/6 |
| | 2250 | 0/10 | 2/10 |
| | 1125 | 0/10 | 0/10 |
| | 563 | 0/10 | 0/10 |

* Five mice died out of 10 inoculated.

IV = intravenous; OS = by stomach tube; IM = intramuscular; IP = intraperitoneal; SC = subcutaneous.

On autopsy the mice were always found emaciated. Apart from occasional grossly observable areas of necrosis in the liver the only changes seen were in the small intestine or in the kidney and abdominal wall following subcutaneous inoculation. The small intestine was often filled with blood or might be so friable as to rupture very readily.

*Microscopically* the lesions produced by intravenous inoculation varied somewhat with different batches although certain lesions were found with all batches. There seemed to be no significant difference

in the tissue changes produced by material of different potency. The most striking lesion occured in the small intestine. Damage was found in the duodenum, jejunum or ileum. In what appeared to be the early changes the submucosa and lamina propria were edematous or thickened, and there was marked monocytic infiltration. The tips of the mucosal villi might be necrotic. In other cases the earliest lesion appeared to be marked hemorrhage into the wall of the intestine and escape of blood into the lumen of the gut. More extreme lesions, which appeared relatively frequently, were on the one hand intussusception and on the other complete gangrene of the intestinal wall. In all, 16 out of 23 mice examined showed one or other of the above lesions, most of them to an extreme degree.

Another severe lesion was not as frequent. This was an arteritis which occurred in medium or small arteries in the lung, pancreas, heart or kidney. The media was necrotic and Weigert's stain showed marked disruption of elastic fibers. The adventitia contained fibrin, red cells, leukocytes and monocytes. This lesion was found in 6 mice. Four others showed foci of necrosis in the heart muscle with hemorrhage and cell infiltration.

In many cases (12 mice) the lungs showed areas with fluid and blood in the alveoli. In the kidney there were different degrees of tubular damage with hyaline or amorphous casts in some tubules. In 3 cases there were areas of necrosis in the liver and in 3 others necrosis of neurones was observed in the hippocampus or in the medulla.

Colon, spleen, salivary glands, lymph nodes, adrenals and bone marrow appeared normal.

In mice dying after subcutaneous injection of streptothricin (see Table 2, Lot STCP) the pathologic picture was entirely different. Macroscopically, as noted above, there was an area of thickening and inflammation surrounding the point of inoculation in the abdominal wall. Apart from this, the only other gross change was that noted in the kidneys which were usually large and pale, and might (in 2 cases) show advanced hydronephrosis. Microscopically, the site of inoculation showed an intense inflammation in the subcutaneous tissue reaching down to the subjacent muscle. The overlying epidermis was greatly thickened, as was the corium. There was an infiltration of fibroblasts and monocytes with occasional binucleated giant cells. Scattered polymorphonuclear leukocytes were not frequent but collections of them were observed forming small or even extensive abscesses. In 1 case such abscesses appeared to be starting around blue-staining, jagged foreign bodies apparently crystalline in nature, but these could not be found in any of the 5 other preparations examined. The intensity of the inflammatory reaction varied but slightly from 1 mouse to another. The kidneys showed quite extensive tubular damage with many hyaline and granular casts. In 1 case, as noted macroscopically, there was advanced bilateral hydronephrosis and in another case unilateral hydronephrosis. In still a third instance, a unilateral dilatation of the pelvis was obvious in the microscopic preparations, although it had not been noted in the gross examination.



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**Summary.** Streptothricin varying in potency from approximately 16% of purity to almost completely purified material has been tested for toxicity in mice by various routes. When the intravenous route is used it is found that the toxic phenomena can be divided into those which occur immediately, and which appear to be due to impurity with a histamine-like activity, and those which come on later and lead to death 2 to 12 days after inoculation. Since the $L_D50$ in units of streptothricin for these delayed deaths does not vary markedly with different preparations from the least to the purest, it is presumed that they are due to the streptothricin itself. Symptoms in the mice include anorexia, labored breathing and, rarely, convulsions.

In those mice which died following intravenous inoculation, lesions were found in the small intestine and in many cases the whole intestinal wall was gangrenous. Other important lesions were an acute arteritis and myocarditis, tubular lesions in the kidney and occasional lesions in the central nervous system and liver. Following subcutaneous inoculation, apart from the local reaction in the abdominal wall at the site of inoculation, the lesions found were confined to the kidney and were considerably more marked in this organ than those noted in mice which had been inoculated intravenously.

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## KLEBSIELLA PNEUMONIÆ BACTERIEMIA SUCCESSFULLY TREATED BY PENICILLIN*

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AND
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Infections with *Klebsiella pneumoniæ* (Friedländer's bacillus) always have been regarded as serious, and with good reason. Statistics reveal mortality figures of 35 to 97% for various types of the infection, including both bacteriemic and non-bacteriemic cases. At one time bacteriemia represented an almost certain fatal outcome, as witness Solomon's[13] series in 1937 and Bullowa's[2] statistics of the same year which revealed 100 and 92% respectively. Later figures were somewhat lower, 75 to 85%, possibly due to the aid of sulfadiazine

* The opinions and assertions contained herein are the private ones of the writers and are not to be construed as official or reflecting the views of the Navy Department or the Naval Service at large.

and sulfapyridine. The experimental studies of the effects of these drugs on animals[1,4] suggest that they may actually exert some curative effect, sulfadiazine being the more potent. However, with mortality figures so appalling, any therapy which might aid in the conquest of this infection should be given adequate trial, without prejudice, and the results made known.

The use of new antibiotic agents in the treatment of infections is undergoing numerous radical modifications. Initial concepts concerning dosage have been revised with consequent changes in the reported effectiveness of the drugs. Penicillin was reported ineffective in the treatment of subacute bacterial endocarditis on the basis of early dosage schedules;[10] yet recent reports indicate a hitherto never-achieved arrest of cases when massive dosage has been applied.[9] The growing literature on penicillin bears constant testimony to the variation in methods of administration, frequency of dosage and other features which must be given firm basis only through the clinical experience of many workers.

It has been a customary and quaint procedure for many writers to classify bacterial response to therapy in accordance with the organisms' acceptance or non-acceptance of the Gram stain. This concept is to be found along with certain other antiquated dicta in many textbooks. Now again, as in the days of enthusiasm for the use of intravenous dyes, we find bacteria being segregated in accordance with this unsupported thesis. The staining property of bacteria neither confers pathogenicity on them nor does it affect their vulnerability. Hence we must regard with some suspicion such far-reaching precepts as appeared this year when Schmitt[11,12] listed as "insusceptible" to penicillin all gram-negative bacilli, including the *Klebsiella pneumoniæ*. Basing the viewpoint only on Fleming's monumental experimental laboratory work[5] and on that of Hobby, Meyer, and Chaffee,[7] and to our knowledge, on no clinical experience, these and other articles gave rise to a new tradition. In a recently published A. M. A. guide[14] to the uses of penicillin, based on the similar list of Dawson *et al.*,[3] under a main heading, "Not Established as Effective for," and a subheading: "All Gram negative bacillary infections" there was listed this full group, including *Klebsiella pneumoniæ*.

In the light of this, it seems desirable to present a case of Klebsiella bacteriemia treated by penicillin with what, we deem, were dramatic results.

**Case Report.** A Merchant seaman, 32 years old, was admitted Aug. 23, 1944, to a U. S. N. Base Hospital in the South Pacific in deep coma. No history was obtainable except that he was in another hospital 2 weeks earlier under the diagnosis of "acute catarrhal fever" and that he had complained of feeling ill the day preceding admission. There was an indefinite report of his having been seen taking some tablets at bedtime and he was discovered unconscious in the morning.

*Physical Examination.* Temp. 103° (axillary). The patient was intensely cyanotic. His breathing was rasping, uneven, and 26 per minute. There was no response to any stimulation. The pupils were small but not pinpoint. The nose showed a crusted purulent discharge. The teeth were dirty and

poorly repaired. The throat was diffusely reddened and there was a swelling in left posttonsillar area. The examination of the heart and lungs was negative but breathing was noisy because of transmitted upper tract mucous rattles. The blood pressure was 138/72. There was a long, left flank scar (later found to be due to exploration after a stab wound). The neurologic examination was negative and all other physical findings were within normal limits.

*Laboratory Data.* Hb., 85%; R.B.C., 4,500,000; W.B.C., 34,000 (neutrophils, 86%; lymphocytes, 12%; eosinophils, 1%; basophils, 1%). Urine: yellow, clear; sp. gr., 1.023; albumin, 0; sugar, 0; micro., occasional leukocyte. Thick smear for malaria, negative. Spinal fluid, pressure 177 mm. of water, clear, colorless. Cell count, 0. Pandy's test, negative. Smear and culture, negative. Chest Roentgen ray, elevation of the right diaphragm. Clear lung fields.

Constant oxygen administration by mask was employed from the time of entry for 48 hours. Two hours after admission, an effort was made to pass a nasal tube to obtain a specimen of the gastric contents. An obstruction was encountered and severe laryngospasm occurred, during which pus appeared in his mouth and on turning him face down several ounces of thick stringy pus poured from his nose and mouth. The passages were cleared by aspiration and a clear view of the throat was obtained. There was a small opening in the swelling behind the left tonsil at the lateral border of the posterior pharyngeal wall. From this pus was escaping.

A blood culture was taken after which he received 5 gm. of sodium sulfadiazine intravenously.

The course from this point is indicated by the following notations:

*8-23-44:* 2100—Temp., 105.4° (rectally). Respirations, 36. Pulse, 150. Condition grave. Fundi—haziness of both nasal disk margins. Very restless.

2300—Penicillin therapy begun (200,000 International units in 1000 cc. 5% glucose in saline given by intravenous drip). Thereafter for 82 hours a continuous intravenous drip of penicillin was maintained introducing about 300,000 units in 24 hours. Each 100,000 units was dissolved in 1000 cc. of 5% glucose in saline.

*8-24-44:* 0800—Respiration, 50. Pulse, 160 and very thready. Skin cyanotic and mottled. Extreme restlessness. Fundi: disk elevation on left, and increase in haziness of nasal disk border on the right. Slight palpebral edema.

1200—A report from the laboratory at this time identified a blood culture growth as *Klebsiella pneumoniæ* (Friedländer's bacillus).

Despite the previously mentioned tradition that penicillin was an ineffective agent *versus* Klebsiella, it was determined to continue the full dosage. The patient's condition appeared desperate.

1500—Color slightly improved. Temp., 102.6° (axillary); pulse, 144; respiration, 48.

*8-25-44:* 0700—Had a very restless night despite nembutal per rectum. Catheterized at 12-hour intervals.

0900—Temp., 103.4° (axillary); pulse, 160; respiration, 32 to 40. Condition worse. Restlessness had resulted in numerous large blisters on the legs, back and buttocks. Spinal fluid, clear, colorless; pressure, 140 mm. of water; laboratory examinations of fluid all negative.

0930—Sodium amytal, 0.3 gm., intravenously for extreme restlessness.

1803—Pentothal sodium, 0.5 gm., intravenously.

2050—Scopolamine, 0.6 mg. (The combination of barbiturate and scopolamine proved effective and was used during the ensuing 24 hours.)

*8-26-44:* 0600—Temperature had fallen steadily. Temp., 99.8° (axillary); pulse, 104; respiration, 28. Responded to stimuli. Swallowed water in sips.

0820—Marked involuntary diarrhea. Coughed and raised sputum.

2200—Slept quietly.

*8-27-44:* 0900—Temp., 99.4° (orally); pulse, 88; respiration, 30. This concluded the intravenous use of penicillin (1,200,000 units had been employed to this point and in a period of 82 hours). Cough continued.

*Roentgen ray* showed small area of consolidation at the left base.

From 8–27 to 8–28, 20,000 units of penicillin were given intramuscularly every 3 hours. From 8–29 to 8–30 the dose was 10,000 units every 3 hours and thereafter until 8–31 it was 10,000 units every 4 hours. The total amount of intramuscular dosage was 530,000 units and the entire amount employed was 1,730,000 units.

On the 4th day of hospital stay the optic nerve heads were normal to ophthalmoscopic view.

Residua such as the abrations and blisters and the pneumonic area cleared promptly and the patient was ambulatory on his 11th hospital day.

A blood culture taken on the 2nd day of the penicillin therapy was negative. Smears from the abscess 1 day after its evacuation showed a mixed flora with scattered encapsulated gram-negative organisms morphologically Klebsiella. The final report on the initial blood culture was "*Klebsiella pneumoniæ* or Friedländer's bacillus confirmed culturally and morphologically. Specific typing sera for Friedländer group was not available."

It was ascertained in the history obtained after the patient's recovery that he had felt very ill the night prior to admission, and had taken 4 or 5 sedative pills, size and nature unknown.

**Discussion.** The events in the clinical progress in this case were confused somewhat by the history of self-administration of a sedative. It is impossible, therefore, to judge whether complete coma was a *bona fide* feature of the infection. The sequence of events in the progress of the case indicates the initial focal point as the pharyngeal abscess, followed by bacteriemia and attendant, but later, pneumonia. Suspicion may well exist that an early cavernous sinus phlebitis was in progress at the time of admission. All fundus signs disappeared with improvement of the patient. Though Klebsiella bacteriemia is not uniformly fatal, especially if there is an accessible primary focus, the extremely rapid cessation of symptoms in a patient so critically ill inclines one strongly to the conclusion that the therapy exhibited had a marked effect. It must be borne in mind that penicillin exerts its action as a bacteriostatic only during bacterial multiplication. Gardner's work[6] revealed that morphologic changes occurred in the numerous types of bacteria tested and even in the group classified as gram-negative—a class which has been regarded as uniformly nonsusceptible. In these last there was noted chiefly cellular elongation. It is not unreasonable to presume that bacteriostasis may reveal itself *in vivo* to be a critical factor, though the noted changes *in vitro* were insignificant. In 1943, Jaffe[8] concluded his report of extrapulmonary Klebsiella infections which recovered under treatment with sulfadiazine on a hopeful note. We quote his final sentence: "Because of a persistent high mortality rate in *Klebsiella pneumoniæ* infections, it is felt that further therapeutic trials should be attempted with the newer sulfonamide compounds and also with the newer antibacterial agents such as gramicidin, penicillin and aspergillin."

With this presentation of a case of severe *Klebsiella pneumoniæ* infection with bacteriemia treated successfully by penicillin, it is hoped that its further use in such conditions may be encouraged despite all previous dicta that the condition would not be responsive.

**Summary.** 1. A case of very severe infection with *Klebsiella pneumoniæ* treated by large doses of penicillin recovered. A pharyngeal

abscess was the initial focus, bacteriemia complicated the condition, and there was probably early cavernous sinus phlebitis and a secondary bronchopneumonia.

2. This appears to be the first record of a case of *Klebsiella pneumoniæ* infection treated by penicillin.

3. The penicillin was administered in direct contradiction to all published formulæ regarding susceptibility of this organism.

4. Since the notoriously fatal character of such infections is recognized, it is hoped that the rapid and dramatic recovery of this patient under penicillin therapy will encourage its further trial in large dosage in future *Klebsiella pneumoniæ* infections.

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## RICKETS IN ICELAND

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In medical literature reference is sometimes made to Iceland as a country in which rickets is unknown. This is a misconception which may be traced back to Icelandic medical authorities from the 18th century, who have been quoted and misquoted ever since.

In a medical survey performed almost a century ago Schleisner[2] noted 7 patients with rickets among a total of 327 patients personally examined by himself. But as he does not mention their age, we cannot know how many of them were children, nor decide whether some of these cases have not been residual malformations after healed rickets.

The first systematic survey of prevalence of rickets was published by Thoroddsen,[4] who found rickets among the children of Reykjavik in 51.5% of children within 2 years of age. These investigations were founded on clinical examinations, and the author stated that undoubtedly the percentage of rickets was actually considerably higher.

There are still some practitioners in Iceland who doubt the conclusion of Thoroddsen's paper. This scepticism may probably be explained by the comparatively rare occurrence of rickets in its most extreme forms, as seen in the industrial cities of Europe. Many a

country doctor can practice for years without seeing such cases. On the other hand, nobody who keeps his eyes open on the streets of Reykjavik can fail to observe the frequency of malformed bones, particularly the legs, which around knees and ankles carry unmistakable signs of healed rickets.

**Material.** A total of 253 children were examined, all in Reykjavik, but 14 failed to appear for final examination, making a total of 239 completed examinations. All the children were from 3 months to 2 years of age. Of this number, 71 were from a health center for children, the remaining 168 we obtained by writing to mothers who had been delivered at the obstetric department of the State hospital in Reykjavik, encouraging them to bring the children to us and have them examined carefully for rickets. All these children were, with 2 exceptions, between 3 and 12 months of age. Most of the children from the health center were more than 1 year old.

**Methods of Examination.** Each child was stripped naked and examined clinically. A case history was taken at the same time and noted whether the child had received any antirachitic treatment. Of each child a Roentgen ray picture was taken of wrist and knee, and in all doubtful cases also of the ankle. As a rule, the changes were more distinct in the ankles than in the wrists. Of the young children, under 1 year of age, we took a picture of the whole crus on which knee and ankle joint could be seen with the entire leg bones. Such pictures were particularly valuable, as changes were frequently seen in the leg bones apart from the joints, particularly in the fibula.

The *clinical examination* was directed to the general condition of the child, noting state of nutrition, anemia, condition of muscles, and so forth, with special attention directed toward the condition of the bones:

1. The fontanelles were examined and if open, their size measured.
2. The cranial bones were examined bimanually. Changes were frequently found, especially in the form of extended flat prominences in the region of the parietal bones, very pronounced in some children. Flattening of the occipital bone and hairlessness at the back of the head was also frequently observed.
3. The chest was carefully observed, for here changes were frequently noted, chiefly in the form of a rachitic rosary and a Harrison's groove, both of which were comparatively frequent. Some children displayed major malformations of the thorax: barrel-shaped chest with flattened sides, of a more or less pronounced pectus carinatum, with protruding sternum.
4. Examination of extremities, with palpation of wrists and inspection, of possible curves of legs.

**Results.** The following table gives a survey of our clinical findings:

TABLE 1.—BONE FINDINGS

| Age | Harrison's groove | | Costochondral prominences | | Parietal prominences | |
|---|---|---|---|---|---|---|
| | + | − | + | − | + | − |
| 3 mos. | 2 | 7 | 6 | 3 | 5 | 4 |
| 4 " | 1 | 3 | 2 | 2 | 3 | 1 |
| 5 " | 5 | 18 | 14 | 9 | 17 | 6 |
| 6 " | 16 | 12 | 21 | 7 | 21 | 7 |
| 7 " | 17 | 25 | 22 | 20 | 24 | 18 |
| 8 " | 3 | 1 | 2 | 2 | 2 | 2 |
| 9 " | 19 | 26 | 24 | 21 | 25 | 20 |
| 10 " | 12 | 9 | 10 | 11 | 12 | 9 |
| 11 " | 7 | 9 | 5 | 11 | 12 | 4 |
| 12 " | 1 | .. | 1 | .. | 1 | |
| 1 yr. | 1 | 44 | 3 | 42 | 12 | 33 |
| 2 yrs. | 3 | 8 | 2 | 9 | 2 | 9 |
| Totals | 87 | 162 | 112 | 137 | 136 | 113 |
| Per cent positive | 36 | | 44 | | 54 | |

*Criteria for Clinical Rickets.* No single sign was considered sufficient for diagnosing rickets clinically, except Harrison's groove. Parietal prominences were not considered sufficient alone, but in combination with a flattened occipital bone or a distinct rachitic rosary were considered sufficient for diagnosing rickets. A distinct rachitic rosary was practically never the only sign of rickets. Parietal prominences and other changes in the cranium or chest could almost without exception be found in addition, to corroborate the diagnosis.

FIG. 1.—Crus from 5 months female. Pronounced rickets. Fibula curved inward. Lower end of tibia inclined inward, causing deformity (varus inclination) of talocrural articulation. Broadening of ossification line of tibia's lower end. Medial condyle of tibia drawn out into a point. Clinically: distinct Harrison's groove and rosary. The child had received no antirachitic treatment.

In a poorly nourished child with distinct signs of rickets we found a rachitic rosary of the special kind which is supposed to be characteristic of scurvy: a bayonet-shaped prominence of the costochondral junction, of such a form that a finger proceeding inward along the surface of the rib falls suddenly down on the cartilage.

In the extremities comparatively slight changes were found clinically. Epiphyseal thickenings, which are so frequently described elsewhere, were not found clinically by us, neither in the wrists nor in other joints.

FIG. 2.—Well calcified bones with straight ossification lines. No rickets. Child, 10 months old, had received vigantol and cod-liver oil for months.

FIG. 3.—Child, 6 months old. No antirachitic treatment. Distal end of ulna cup-shaped from calcium resorption. Calcium shadow clouded on ulna, but fairly distinct on radius.

Roentgen ray examinations were at first made of right wrist and left knee of each child. But we soon realized how valuable a picture of the ankle was, and added it in all doubtful cases where we had not taken a picture of the whole crus.

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The Roentgen ray pictures were interpreted according to the findings described by Wimberger[5] and Lindblom.[1] Our principal criterion was the aspect of the line of calcification at the epiphyses: instead of the clear-cut, straight and narrow line of normally growing bone, the calcification line is seen more like an indistinct shadow, indented and broken and in severe cases no calcification can be seen, but only a broad band of uncalcified tissue, and at last the distal end of the bone becomes broader with a concave surface owing to absorption of calcium. Correspondingly and preceding these changes, the spongiosa network is blurred, owing to insufficient calcium content, and the diaphysis loses in strength and straightness, particularly in slender bones like the fibula of infants, which was frequently curved inward toward the tibia. In general the fibula seemed to calcify later and less than the tibia, and the ossification lines were always more indistinct in the fibula than the tibia, in all rachitic cases, although they were just as distinct in non-rachitic cases. This suggested that the bone which is less exposed to strain and exercise did receive less calcium than the one which had a more pronounced functional stress.

In the knees we observed changes of a characteristic appearance: at the medial articulate surface of the tibia the bone appeared to be broadened and flattened in such a way that the median condyle came to be drawn out into a point (Fig. 1). In some cases a similar formation was seen on the lateral condyle of the tibia, but rarely on the medial condyle of the femur. Probably these formations are due to compression of young cartilage and osteoid tissue which is presumably weakened by other reasons, particularly want of vitamin C, for such changes are considered a sign of scurvy.

On the whole, Roentgen ray pictures conformed well with the clinical findings, but in a few cases no clear Roentgen ray changes were found in cases where clinical signs were unmistakable. All the Roentgen ray readings were made without knowledge of the clinical findings, in order to obtain an independent Roentgen ray judgment uninfluenced by the clinical findings. By comparing the two examinations a final diagnosis was made. The following table gives a survey of our findings:

TABLE 2.—SURVEY OF CLINICAL AND ROENTGEN RAY FINDINGS

| Age (mos.) | Clinical diagnosis Rickets | | | Roentgen ray diagnosis Rickets | | | Final diagnosis Rickets | | | Rickets (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| | + | − | Healed | + | − | Healed | + | − | Healed | |
| 3 | 4 | 3 | .. | 6 | 1 | .. | 6 | 1 | .. | 86 |
| 4 | 3 | 1 | .. | 3 | 1 | .. | 4 | .. | .. | 100 |
| 5 | 20 | 2 | .. | 19 | 2 | 1 | 20 | 1 | 1 | 95 |
| 6 | 23 | 5 | .. | 25 | 2 | 1 | 25 | 3 | .. | 89 |
| 7 | 32 | 10 | .. | 34 | 7 | 1 | 33 | 8 | 1 | 81 |
| 8 | 4 | 1 | .. | 3 | 1 | 1 | 3 | 1 | 1 | 80 |
| 9 | 26 | 16 | .. | 30 | 11 | 1 | 33 | 7 | 2 | 83 |
| 10 | 16 | 4 | .. | 15 | 2 | 3 | 15 | 1 | 4 | 95 |
| 11 | 10 | 6 | .. | 13 | 2 | 1 | 11 | 4 | 1 | 75 |
| 12 | 1 | .. | .. | .. | 1 | .. | .. | .. | 1 | |
| 18 | 8 | 34 | .. | 15 | 23 | 4 | 15 | 23 | 4 | 45 |
| 24 | 2 | 8 | .. | 3 | 5 | 2 | 3 | 5 | 2 | 50 |
| Totals | 149 | 90 | .. | 166 | 58 | 15 | 168 | 54 | 17 | |
| Rickets | 63% | | | 75% | | | 77% | | | |

The finding of 77% of all children between 3 months and 2 years affected with rickets reveals a considerably higher percentage of rickets than Thoroddsen found. Our clinical examination alone showed a higher percentage of rickets than Thoroddsen found, but she remarked (l.c.) that her figures were rather too low than too high.

*Influence of Cod-liver Oil and Ultraviolet Light.* Information was obtained from the mothers as to whether cod-liver oil had been administered or the child had been exposed to irradiation by ultraviolet light. The following table gives a survey of this enquiry:

TABLE 3.—EFFECT OF COD-LIVER OIL AND ULTRAVIOLET LIGHT

| Treatment | Rickets | | | Free of rickets (%) |
|---|---|---|---|---|
| | + | − | Healed | |
| Cod-liver oil | 99 | 41 | 12 | 34 |
| Ultraviolet irradiation, 7 times or more | 15 | 18 | 6 | 62 |
| No treatment | 44 | 4 | 0 | 8 |

**Comment.** This survey indicates that practically every child will develop rickets in this country unless it receives some kind of prophylactic treatment, either D vitamin in some form or direct irradiation.

In this survey we saw few bones with clear straight calcification lines and distinct spongiosa structure, and such findings were chiefly limited to children who had received artificial sun baths for a longer period. If such bones had been taken as a norm, all the children examined would have been considered rachitic, with very few exceptions.

However, although the question as to what should be looked upon as a norm in growing bones is a debatable one, there can be no doubt that rickets is very prevalent in Iceland, although high degrees of it are rare. M. B. Schmidt[3] has pointed out that rickets may present different aspects in different localities. Here, the disease seems mainly to affect the cranial bones and the ribs, which may show very conspicuous changes although no clinical and even no Roentgen ray changes may be found in the long bones of the extremities.

The occurrence of rickets in spite of cod-liver oil is apparently due to insufficient dosage. Most children receive only 1 teaspoonful a day, containing 2 to 3 gm. of oil which contains 200 to 250 I.U. per gm. or a daily dose of 400 to 750 I.U. This dose is less than half of what is regarded as necessary for the average child (1500 I.U.), although much higher doses may be required in some cases. It is, therefore, not surprising that irradiation gave the best results.

Owing to the long dark winter months in this country, specific antirachitic therapy is required during this period, for the long days of summer do not afford adequate protection, no matter how well utilized, against the long and dark winter. Higher doses of cod-liver oil than have been commonly used up to this time are required, and the value of ultraviolet irradiation is being more and more appreciated by the population.

**Summary.** A survey was made on 253 children in Iceland, all between 3 months and 2 years of age. Each child was examined clinically and with Roentgen rays of wrist and knee, usually also including crus and ankle.

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The clinical examination showed definite signs of rickets in 66%. Of these, 35% had a visible Harrison's groove, 44% a rachitic rosary, and definite signs of cranial rickets were found in at least 54%. Roentgen ray photographs showed signs of rickets in 75% of the children.

The final result, obtained by comparing clinical and Roentgen ray examination, showed an incidence of 77% with rickets.

These results dismiss the widespread belief that rickets is unknown in Iceland.

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## HEMORRHAGIC TELANGIECTASIA WITH PULMONARY ARTERY ANEURYSM: CASE REPORT

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Hereditary hemorrhagic telangiectasia (Rendu,[21] Osler,[17] Weber[28]) is an uncommon disease characterized by the familial occurrence of anomalous groups of capillary and venous dilatations which are subject to repeated hemorrhage. The following case illustrates many typical aspects of this disease and shows, in addition, some unusual features.

**Case Report.** E. D., No. 389283, a 56 year old factory worker was admitted to the University Hospital on January 17, 1944, complaining of recurrent abdominal pain, weakness, and poor vision. His general health had been good during his earlier life but for 2 years he had been unable to work.

When about 14 years of age, after a fall and slight injury to his nose, he began to have brisk nosebleeds once or twice every week, losing an ounce or more of blood each time. The nosebleeds continued throughout the years, later becoming less profuse but then occurring nearly every day. No other source of bleeding was noted, nor was there excessive bleeding from cuts and scratches.

When about 35 years of age he had for a time recurrent epigastric pain between meals and at night, which was relieved by the ingestion of food and soda. Roentgen examination at a Marine Hospital was reported to reveal a peptic ulcer, and he was treated for 6 weeks with a milk diet and Sippy powders. The symptoms subsided and did not recur.

He was first admitted to the University Hospital on September 15, 1996, 6 weeks after the onset of dull, sometimes colicky, abdominal pain referred to an area about and below the umbilicus. The pain occurred at various times during the day and night without relation to meals, exertion, or other external factors. There was no relief following ingestion of food or alkalies. He had noted no change in bowel habits, but some of his stools were black. Two weeks before admission he became weak and short of breath. With more than slight exertion he had palpitation, dyspnea, and chest pain. Pitting edema of the legs and persistent vomiting developed shortly before his admission to the hospital.

Physical examination showed a well developed and well nourished but very pale white male. About the lips, tongue and the oral mucous membranes there were many small, reddish macules 1 to 3 mm. in diameter. The blood pressure was 155/55 mm. Hg. The thorax was somewhat asymmetrical. The heart was not enlarged and the rate and rhythm were normal. An early systolic murmur was audible at the cardiac apex. The percussion note was resonant over both lung fields and there were no thrills. A continuous murmur, entirely separate from the heart sounds, was heard in a localized area in the 5th intercostal space below and outside the right nipple. The murmur was accentuated late in systole, became very faint during diastole, and was much louder after inspiration. There was pitting edema over the lower legs.

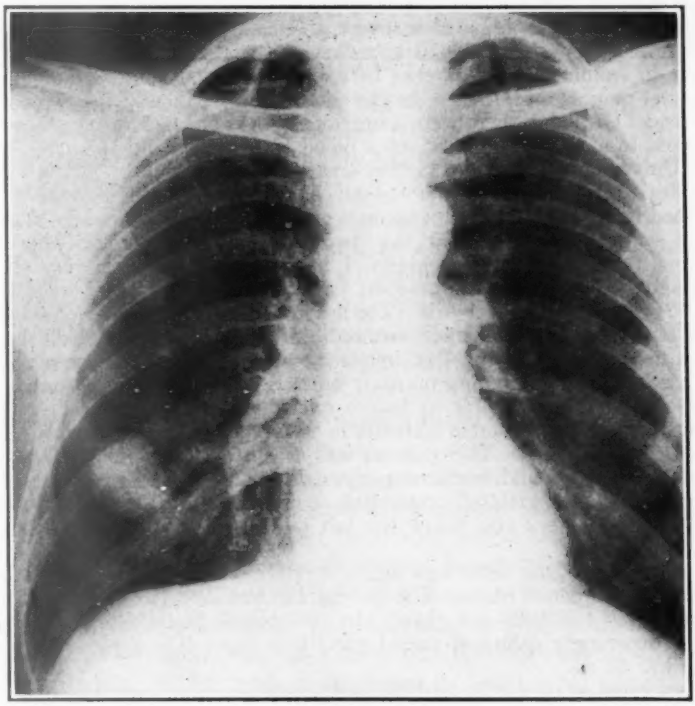

FIG. 1.—Chest roentgenogram on the first admission showing the rounded opacity anteriorly in the right lung and the vascular shadow connecting it with the hilum. A loud murmur was audible over the adjacent chest wall.

Examination of the blood showed a hemoglobin value of 26% (Sahli) and a red cell count of 3,100,000 per c.mm. Urinalysis and several Kahn tests were negative. Gastric analysis revealed no free hydrochloric acid in the gastric contents after subcutaneous injection of histamine. Several stool specimens gave strongly positive guaiac reactions. An electrocardiogram was not definitely abnormal. Sound records from the heart and right chest area confirmed the auscultatory findings but added no further information. A chest roentgenogram showed a sharply circumscribed nearly round, homogeneous opacity about 4 cm. in diameter in the right middle lobe area (Fig. 1). Extending from the opacity to the pulmonary hilum there was a prominent vascular trunk. On fluoroscopy the tumor moved during inspiration and expiration with respect to the chest wall. Slight expansile pulsation was observed fluoroscopically and this was confirmed by kymographic films. Roengten examination of the gastro-intestinal tract revealed no abnormalities.

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The patient received 4 blood transfusions during his hospital stay and ferrous sulfate by mouth. He was discharged after 5 weeks, feeling entirely well.

At home he resumed work and for nearly 5 years considered himself well. Nosebleeding continued as before, nearly every day. In the fall of 1942 there was a recurrence of mid-abdominal pain coming at various times during the day and night without relation to meals and not relieved by food or alkalies. Black stools were noted and he soon became weak, pale, dizzy when standing, and short of breath when active. He was taken to a local hospital where a blood transfusion was given, after which he was discharged with a box of tablets containing iron. He gradually improved during the following months but was never well, being able to work only about one-third of the time at easy jobs. Several months later another identical episode of abdominal pain followed by tarry stools and symptoms of a severe anemia occurred, with slow and incomplete recovery after 2 blood transfusions.

Early in January 1944, 2 weeks before his second hospital admission, the abdominal pain again returned and he soon became pale and too weak to get out of bed. On 1 day there were 3 urgent passages of black, tarry stools. He was taken to a local hospital, given a blood transfusion, and then transferred to the University Hospital for further treatment.

Physical examination on the second hospital admission showed a well-developed male who appeared weak and chronically ill. There were bilateral, mature, senile cataracts. About the lips, tongue and nasal septum there were numerous reddish-blue telangiectasia, 1 to 3 mm. in diameter, very slightly raised above the level of the mucosa. A few similar structures were visible over the forearms and finger-tips. The heart was borderline in size, and at the apex a blowing systolic murmur was audible. Over both lung fields the percussion note was resonant, and fremitus and breath sounds were normal. A moderately loud, continuous murmur, entirely separate from the sounds over the precordium, was audible as before over the right anterior chest, being loudest in an area 3 to 4 cm. in diameter in the 5th intercostal space just outside the mid-clavicular line. The murmur was accentuated in late systole with a faint, low-pitched sound continuing through diastole. The murmur became nearly twice as loud with full inspiration as during expiration. The tip of the spleen was palpable 2 cm. below the left costal margin at the end of deep inspiration.

Urinalysis and Kahn tests were again negative and the stools gave strongly positive tests for occult blood. The hemoglobin was 30% (4.8 gm.) and the red cell count was 4,500,000 per c.mm. In the stained blood film the red cells appeared extremely pale and varied greatly in size. The mean corpuscular volume was 65 $c\mu$.

A chest roentgenogram showed the previously described opacity in the right lung field and the prominent vascular shadow connecting it with the pulmonary hilum. There had been no more than a slight increase in size during the previous 7 years. On fluoroscopy the tumor appeared to change slightly in shape during respiration and to become denser during inspiration. There were no other definite abnormalities in either lung, although 2 small somewhat variable shadows were present that were difficult to interpret. Roentgen examination of the gastro-intestinal tract was negative.

A gastroscopic examination (Dr. H. M. Pollard) provided a satisfactory view of the interior of the stomach up to and including the pyloric valve. The mucosa was definitely pale. Several clusters of telangiectasia were visible along the lesser curvature and on the anterior wall, and a few were present in the antrum and one on the pyloric valve. Each telangiectasis was circular, 2 to 3 mm. in diameter, sharply circumscribed, and intensely red. The dilated vessels were level with the surface of the mucosa and did not protrude into the lumen. Fresh blood oozed from the gastric mucosa in 2 or 3 areas.

A sigmoidoscopy was performed and no telangiectasia were seen.

The patient was given ferrous sulfate 0.6 gm. 3 times daily. After 1 week the red cell count had risen to 5,000,000, the hemoglobin to 57% (8.9 gm.) and the mean corpuscular volume to 70 $c\mu$. At the end of 2 weeks the red cell

count was 5,200,000, the hemoglobin 69% (10.7 gm.), and the mean corpuscular volume 79 $c\mu$. An uneventful cataract extraction was then carried out.

When discharged home he was advised to supplement his daily diet with ferrous sulfate permanently. On a check-up examination 3 months later he reported that his general health was vastly improved. He had had an occasional episode of abdominal pain but no tarry stools. One nosebleed had been profuse and had lasted 5 days. Physical examination showed nothing new except greatly improved general health. The R.B.C. count had increased to 5,700,000, the hemoglobin to 109% (17.1 gm.) and the average cell volume to 95 $c\mu$. A second cataract operation was performed without complication.

The patient's parents were over 80 years of age, living and well. He was one of 8 children, and had 1 daughter and 1 granddaughter. None of his relatives were known to have had frequent epistaxes or other types of abnormal bleeding, nor to have had visible telangiectasia. None of his family were available for examination.

The general clinical features of hereditary hemorrhagic telangiectasia have been presented in many publications.[1,4,10,12,14–16,18,19,25–27] The hereditary nature of the malady has been of most general interest. The sexes are equally affected, and both males and females may transmit the disease to their offspring. In many families the disease appears to be inherited as a dominant characteristic but several instances of skipped generations in afflicted families have been recorded (Osler,[17] Weber,[28] Steiner,[25] Audry,[2] Fitz-Hugh,[6] Foggie,[8] Edel, Van Gilse and Postma,[4] Hurst and Plummer,[13] and Singer and Wolfson[24]). It is believed that this "atavistic" or recessive hereditary transmission may account for the many otherwise typical cases, such as the one reported here, in which no positive family history can be obtained.[9]

Epistaxis is the commonest symptom, since delicate, easily traumatized telangiectasia occur most frequently on the nasal septum, but bleeding from the skin or oral mucous membranes occurs in the majority of patients and may even be the exclusive site of hemorrhage. The telangiectasia usually do not appear before the age of puberty. In the 3rd and 4th decades of life they become more numerous and more subject to hemorrhage. The individual groups of dilated vessels are not entirely permanent structures but tend to vary from time to time in number, in size, and in tendency to bleed. An anemia severe enough to be incapacitating often results from the long-continued blood loss, and a number of fatal hemorrhages have been reported.

The frequency of internal bleeding in patients with hereditary hemorrhagic telangiectasia has been emphasized by several recent authors. Hematemeses, hemoptyses, melena, hematuria, and even cerebrovascular accidents have many times been attributed to bleeding from telangiectasia, although clinical or pathologic proof has been infrequent. One of Osler's[17] patients died of carcinoma of the stomach, and necropsy disclosed the presence of many gastric telangiectasia. Boston[3] reported 3 patients with hemorrhagic telangiectasia who had had repeated attacks of gastric hemorrhage. Surgical exploration was necessary to control hemorrhage in one of his patients and gastric bleeding from a small cluster of abnormal vessels was found. One of Fitz-Hugh's[7] patients had had hemoptyses, and bronchoscopy revealed distinct telangiectasia which bled with the slightest pressure in the trachea and in the left bronchus. Telangiectasia were also seen in the

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lower colon by sigmoidoscopy and their histologic nature was confirmed by biopsy. Four years later, however, at autopsy there were no telangiectasia visible in either the respiratory passages or in the gastro-intestinal tract. Hurst and Plummer,[13] also, emphasized gastro-intestinal hemorrhage as a complication of this disease. In 3 typical cases, and in 1 in which there was no confirmatory family history, telangiectasia were seen by sigmoidoscopy. Renshaw[22] was the first to see hemorrhagic telangiectasia in the stomach by gastroscopy and gave an excellent description of their appearance. His patient had had episodes of severe gastro-intestinal bleeding for 12 years with recurrent severe anemia. Roentgen examination of the stomach and colon was negative and telangiectasia were not seen by sigmoidoscopic examination. No family history of the disease was mentioned. Griggs and Baker[11] reported 3 patients with hereditary hemorrhagic telangiectasia whose presenting complaints were gastro-intestinal bleeding. The exact origin of the bleeding was not discovered, since roentgen examination was negative in all cases and in the one patient in whom gastroscopic and sigmoidoscopic examination were done no telangiectasia were seen. All of their patients, as the one in the present report had abdominal distress which recurred during the periods of active bleeding.

Detailed pathologic studies in hereditary hemorrhagic telangiectasia have been very few. The 9 published necropsy reports were recently reviewed by Schuster[23] in reference to the multiple vascular abnormalities which occurred in a typical case in which he performed a complete postmortem examination. Telangiectasia in his case were present in the skin, nose, mouth, pharynx, larynx, trachea, stomach and duodenum. None were present in the bronchi, colon, rectum, kidneys, or serous membranes. Dilated and distorted fibrotic veins were present in the upper lobe of one lung and beneath the surface of the liver capsule. A unique feature was the presence of multiple aneurysms of the splenic artery each about the size of a hazel-nut. The relation of these vascular anomalies to the capillary and venous dilitations which characterize this disease is still uncertain.

Aneurysm of the pulmonary artery has not been reported previously in any patient with hereditary hemorrhagic telangiectasia. The roentgen appearance and physical findings in our case strongly suggest an arterial dilatation comparable to the splenic aneurysms described by Schuster, although a vascular tumor with arteriovenous communication might possibly account for the findings. Thoracotomy and lobectomy was considered at the time of the first admission of our patient. The almost complete stability of the lesion for over a period of 7 years indicated a better prognosis than was first suspected and operation was finally considered inadvisable.

The treatment of hereditary hemorrhagic telangiectasia is difficult and somewhat unsatisfactory. Trauma, a factor of importance in the development of the telangiectasia[12] as well as in inducing bleeding from them, can be avoided to some degree with respect to exposed surfaces. Iron is the only medication of proved value, and in those subject to chronic blood loss it should be used continuously. The local treat-

ment of nasal telangiectasia with chromic acid,[12] radium, or electrodesiccation[5] has been of definite benefit in some patients in the control of epistaxis. An inflated finger cot has long been recommended as the most effective method of controlling profuse nasal hemorrhage.[17] No satisfactory method of dealing with internal hemorrhage other than treatment of the anemia and use of blood transfusions when necessary has been devised.

**Summary.** A case is reported of a patient with hemorrhagic telangiectasia who had suffered from repeated epistaxis from the age of 14, and in later life from gastro-intestinal hemorrhage severe enough to produce a severe, incapacitating anemia. Multiple gastric telangiectasia were seen by gastroscopic examination. An aneurysm of the pulmonary artery was present which did not increase appreciably in size during a period of over 7 years observation.

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## TISELIUS ELECTROPHORESIS STUDIES OF PLASMA PROTEINS IN ADDISON'S DISEASE

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The importance of the adrenal cortex in maintaining normal plasma composition is well established. Several crystalline preparations,

notably desoxycorticosterone acetate and corticosterone, are capable of maintaining a normal plasma electrolyte concentration and blood volume in the adrenalectomized animal and the patient with Addison's disease. Levin and Leathem,[2] and Hartman *et al.*[1], reported plasma protein studies in adrenalectomized animals. They found a lowered albumin level in the plasma of dogs and cats. In experiments reported by Hartman *et al.*[1] the low albumin-globulin ratio was found to persist whether the adrenalectomized animal was maintained on whole adrenal extract, desoxycorticosterone acetate, sodium salts, Hartman's "sodium factor," or "cortin."

The plasma protein fractionations mentioned were determined by the "salting out" method, which is open to considerable error. The present studies were carried out using the Tiselius electrophoresis method, which provides a more accurate and complete fractionation of the various plasma proteins.

**Subjects, Materials and Methods.** Nineteen patients with proved Addison's disease were studied. The diagnosis was established by physical examination and confirmed by pertinent laboratory findings such as low serum sodium, high serum potassium, low indices with the Robinson-Power-Kepler test, and hemoconcentration. Of these patients, 6 were followed over a period of months to determine what changes occurred in the plasma protein picture during adrenal insufficiency and after various types of replacement therapy.

The Tiselius electrophoresis technique as modified by Longsworth was used.[5] Total and non-protein nitrogen were determined by the Pregl modification of the micro-Kjeldahl method.[6] A detailed description of methods used in this laboratory has been published.[3]

Desoxycorticosterone acetate, administered either in an oil base or in pellets, whole beef adrenal extract, and pig adrenal extract were the materials used in treatment. Beef adrenal extract in an aqueous base was administered intramuscularly usually twice daily. Hog adrenal extract in an oil base was injected intramuscularly once daily. Pellets of desoxycorticosterone acetate were implanted subcutaneously. Replacement of pellets was usually required in 9 to 12 months.

**Results.** The results of studies made when definite signs of adrenal insufficiency were present are summarized in Table 1. In 4 of the 7 cases the total plasma protein fell in the upper normal range. Hemoconcentration was present. It is evident that this makes the plasma protein levels appear higher than they would be if the plasma volume had been normal. It also means that since hemodilution takes place during therapy the increase in the total circulating plasma protein is greater than would be indicated by the plasma protein concentration level alone, and the amount of albumin necessary to bring the concentration to normal levels is greater than would be indicated if plasma volume is not considered. In 1 case the total protein was very low, being 4.54 gm. per 100 ml. This patient was extremely emaciated, which probably accounted for the severity of the protein depletion. In all studies the percentage of albumin was low, and in 5 cases the total protein in gm. per 100 ml. was below normal limits. There was no consistent increase in any globulin fraction.

Table 2 summarizes the data obtained on 5 of these patients after months of therapy, and on 4 others repeatedly studied, Cases 1 to 4

showed a definite increase in the percentage of albumin after amelioration of symptoms of adrenal insufficiency and during good maintenance.* In no case was the albumin restored to normal levels when the patient was maintained on desoxycorticosterone acetate alone or with small supplementary amounts of adrenal extract. When Case 5 received 15 ml. of adrenal extract in divided doses each day for 4 weeks, the protein distribution became entirely normal. When the extract was changed to hog adrenal extract for 3 weeks, the normal distribution was maintained. Case 7 also showed some increase in the percentage of albumin over that attained with desoxycorticosterone acetate when adrenal extract was used for a long time. The normal level, however, was never attained. Treatment with hog adrenal extract had no beneficial effect; the albumin percentage after 13 weeks closely approximated that observed when the patient received desoxycorticosterone acetate.

Case 6 may possibly have shown a slight increase in albumin percentage when receiving hog adrenal extract. Cases 8 and 9 showed no further improvement in the plasma albumin level when adrenal extract was added to the treatment.

Table 3 summarizes the data on the remaining 9 cases. Case 12 was especially interesting, since the patient appeared to have absolutely complete replacement as judged by physical reactions and sense of well-being when maintained on desoxycorticosterone acetate. He was the only one who had an entirely normal protein distribution when receiving desoxycorticosterone acetate alone. Case 12 was also especially well maintained by desoxycorticosterone acetate, and the protein distribution was nearly normal.

**Discussion.** It is altogether possible that insufficient dosage was responsible for the failure of the plasma protein picture to be restored to normal in some patients treated with adrenal extract. On the other hand, they appeared to be well maintained clinically. It is possible that the factors essential for maintenance of normal protein distribution were not present in sufficient amounts, while principles physiologically active in other ways, factors regulating salt and water balance or carbohydrate metabolism, were administered in adequate quantities.

In Case 2 lack of any immediate alteration in protein distribution during treatment with very large amounts of adrenal extract would indicate that, at least in the patient with Addison's disease, no stores of albumin are readily available to be brought forth after hormone injection, or that albumin and globulin stores are released at such a rate that the distribution is unaltered. The latter assumption seems rather unlikely. Between the first two studies in Case 2 the volume of circulating plasma increased by 12.5% as judged by the decreased hematocrit value, and the plasma protein concentration fell 20%. Estimation of modifications in circulating plasma volume based on

* Maintenance of a normal serum electrolyte level, an essentially normal blood pressure, absence of edema or puffiness and nausea, a good appetite, normal or almost normal energy and endurance and a sense of well-being.

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TABLE 1.—TISELIUS PROTEIN DISTRIBUTION IN ADRENAL INSUFFICIENCY

| Case No. | Treatment | Degree of insufficiency | Total protein (gm./100 ml.) | Albumin | | α-globulin | | β-globulin | | γ-globulin | | Fibrinogen | | Blood pressure |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Gm./100 ml. | % total protein | Gm./100 ml. | % total protein | Gm./100 ml. | % total protein | Gm./100 ml. | % total protein | Gm./100 ml. | % total protein | |
| 21 normal controls | .... | Average | 6.51 | 4.09 | 62.7 | 0.47 | 7.2 | 0.81 | 13.1 | 0.77 | 11.7 | 0.33 | 5.4 | |
| | | range | 5.94–7.82 | 3.72–5.11 | 60.1–67.2 | 0.39–0.66 | 6.0–8.7 | 0.65–1.07 | 11.0–15.9 | 0.60–0.91 | 8.6–14.8 | 0.16–0.48 | 2.8–7.2 | |
| 1 | None | Extreme | 7.04 | 3.29 | 46.8 | 0.72 | 10.2 | 1.02 | 14.5 | 1.39 | 19.7 | 0.65 | 8.8 | 86/? |
| 2 | None | Extreme | 6.82 | 3.26 | 47.8 | 0.82 | 12.0 | 1.13 | 16.5 | 0.78 | 11.5 | 0.83 | 12.2 | 110/70 |
| 3 | 5 ml. adrenal extract per day, 2 weeks | Moderate | 6.08 | 2.66 | 43.6 | 0.81 | 13.4 | 0.93 | 15.3 | 1.03 | 17.0 | 0.65 | 10.7 | 96/50 |
| 4 | 1-2 ml. adrenal extract per day, 4 days | Mild | 5.98 | 3.30 | 55.1 | 0.39 | 6.5 | 0.67 | 11.2 | 1.06 | 17.9 | 0.56 | 9.3 | 96/68 |
| 5 | None | Extreme | 7.21 | 4.01 | 55.6 | 0.46 | 6.4 | 1.04 | 14.4 | 1.21 | 16.7 | 0.49 | 6.9 | 80/56 |
| 6 | None | Moderate | 7.22 | 3.77 | 52.2 | 0.45 | 6.1 | 2.00 | 27.8 | 0.57 | 7.9 | 0.45 | 6.2 | 90/60 |
| 7 | None | Extreme | 4.54 | 2.39 | 52.7 | 0.43 | 9.4 | 0.72 | 15.8 | 0.53 | 11.7 | 0.47 | 10.4 | 70/35 |

TABLE 2.—EFFECT ON TISELIUS PLASMA PROTEIN DISTRIBUTION OF ADDISON'S PATIENTS OF VARIOUS TYPES OF REPLACEMENT THERAPY.

| Case No. | Treatment | Period treated (wks.) | Maintenance | Total protein (gm./100 ml.) | Albumin | | α-globulin | | β-globulin | | γ-globulin | | Fibrinogen | | Blood pressure |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Gm./100 ml. | % total protein | Gm./100 ml. | % total protein | Gm./100 ml. | % total protein | Gm./100 ml. | % total protein | Gm./100 ml. | % total protein | |
| 1 | None | .. | Extreme insuffi. | 7.04 | 3.29 | 46.8 | 0.72 | 10.2 | 1.02 | 14.5 | 1.39 | 19.7 | 0.65 | 8.8 | 86/? |
| | Desoxycorticosterone acetate (pellets 1 wk.) | 6 | Undertreatment | 6.31 | 3.50 | 55.6 | 0.56 | 8.8 | 0.91 | 14.4 | 1.02 | 16.1 | 0.32 | 5.1 | 90/60 |
| | Desoxycorticosterone acetate pellets | 32 | Fair maint. | 6.09 | 3.50 | 57.4 | 0.44 | 7.3 | 0.68 | 11.2 | 0.98 | 16.0 | 0.49 | 8.1 | 110/80 |
| 2 | None | .. | Extreme insuffi. | 6.82 | 3.26 | 47.8 | 0.82 | 12.0 | 1.13 | 16.5 | 0.78 | 11.5 | 0.83 | 12.2 | 110/70 |
| | 270 ml. adrenal extract, 19 mg. desoxycorticosterone acetate | 1 | Improvement | 5.42 | 2.50 | 46.1 | 0.86 | 15.8 | 0.87 | 16.1 | 0.55 | 10.2 | 0.64 | 11.8 | 86/74 |
| * | 5 ml. adrenal extract, 2.5 mg. desoxycorticosterone acetate per day | 6 | Fair maint. | 5.54 | 2.89 | 52.2 | 0.64 | 11.5 | 0.85 | 14.8 | 0.91 | 15.7 | 0.67 | 11.6 | 124/80 |
| 3† | 5 ml. adrenal extr. per day | 2 | Fair maint. | 6.08 | 2.66 | 43.6 | 0.81 | 13.4 | 0.93 | 15.3 | 1.03 | 17.0 | 0.65 | 10.7 | 96/50 |
| | Desoxycorticosterone acetate pellets | 30 | Good maint. | 6.02 | 3.17 | 52.7 | 0.63 | 10.5 | 0.85 | 14.1 | 0.95 | 15.7 | 0.42 | 7.0 | 105/70 |
| | Desoxycorticosterone acetate pellets | 38 | Good maint. | 6.17 | 3.35 | 54.3 | 0.71 | 11.5 | 0.86 | 14.0 | 0.88 | 14.2 | 0.37 | 6.0 | 107/70 |
| 4 | 1–2 ml. adrenal extr., 6 cortalex tablets per day | 4 | Mild insuffi. | 5.98 | 3.30 | 55.1 | 0.39 | 6.5 | 0.67 | 11.2 | 1.06 | 17.9 | 0.56 | 9.3 | 96/68 |
| | Desoxycorticosterone acetate pellets | 13 | Good maint. | 6.08 | 3.55 | 58.1 | 0.37 | 6.1 | 0.73 | 12.0 | 0.82 | 13.4 | 0.63 | 10.4 | 122/80 |
| 5 | None | .. | Extreme insuffi. | 7.21 | 4.01 | 55.6 | 0.46 | 6.4 | 1.04 | 14.4 | 1.21 | 16.7 | 0.49 | 6.9 | 80/56 |
| | Desoxycorticosterone acetate, dosage varied | 12 | Mild insuffi. | 7.03‡ | 4.07 | 58.0‡ | 0.44 | 6.2 | 1.22 | 17.4 | 1.30 | 18.4 | .. | .. | 118/70 |
| | Desoxycorticosterone acetate, 7.5 ml. adrenal extr. per day | 4 | Good maint. | 6.64 | 3.78 | 56.9 | 0.45 | 6.7 | 0.82 | 12.4 | 1.14 | 17.3 | 0.45 | 6.7 | 134/80 |
| | 7.5 ml. adrenal extr. twice a day | 4 | Good maint. | 6.50 | 4.03 | 61.9 | 0.44 | 6.8 | 0.92 | 14.2 | 0.84 | 12.9 | 0.27 | 4.2 | 116/76–124/80 |
| | 2 ml. hog extr. per day | 3 | Good maint. | 7.10 | 4.26 | 60.0 | 0.44 | 6.2 | 0.91 | 12.9 | 0.97 | 13.6 | 0.52 | 7.3 | 115/80 |
| 6 | Desoxycorticosterone acetate pellets | 8 | Good maint. | 6.18 | 3.37 | 54.6 | 0.40 | 6.4 | 1.07 | 17.3 | 0.81 | 13.2 | 0.53 | 8.5 | 138/90 |
| § | Desoxycorticosterone acetate pellets, 7.5 ml. adrenal extr. per day | 4½ | Good maint. | 5.97 | 3.27 | 54.8 | 0.38 | 6.3 | 0.99 | 16.6 | 0.75 | 12.5 | 0.58 | 9.8 | 132/80 |
| | Desoxycorticosterone acetate pellets, 7.5 ml. adrenal extr. per day | 4 | Good maint. | 6.05 | 3.06 | 50.6 | 0.39 | 6.4 | 1.07 | 17.6 | 1.21 | 20.0 | 0.32 | 5.4 | 134/80 |
| | Desoxycorticosterone acetate pellets, 4 ml. adrenal extr. every other day | 52 | Good maint. | 6.62 | 3.60 | 54.2 | 0.48 | 7.3 | 1.03 | 15.6 | 1.07 | 16.2 | 0.44 | 6.7 | 120/82 |
| ** | 1 ml. hog extr., 2 mg. de- | 4 | Overtreatment | 6.24 | 3.35 | 53.6 | 0.48 | 7.8 | 0.96 | 15.4 | 1.01 | 16.2 | 0.44 | 7.0 | 105/72 |

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| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| § | Desoxycorticosterone acetate pellets, 7.5 ml. adrenal extr. per day | 44 | Good maint. | 5.97 | 3.27 | 54.8 | 0.38 | 6.3 | 0.99 | 16.6 | 0.75 | 12.5 | 0.58 | 9.8 | 132/80 |
| | Desoxycorticosterone acetate pellets, 7.5 ml. adrenal extr. per day | 4 | Good maint. | 6.05 | 3.06 | 50.6 | 0.39 | 6.4 | 1.07 | 17.6 | 1.21 | 20.0 | 0.32 | 5.4 | 134/80 |
| | Desoxycorticosterone acetate pellets, 4 ml. adrenal extr. every other day | 52 | Good maint. | 6.62 | 3.60 | 54.2 | 0.48 | 7.3 | 1.03 | 15.6 | 1.07 | 16.2 | 0.44 | 6.7 | 120/82 |
| ** | 1 ml. hog extr., 2 mg. desoxycorticosterone acetate per day | 4 | Overtreatment | 6.24 | 3.35 | 53.6 | 0.48 | 7.8 | 0.96 | 15.4 | 1.01 | 16.2 | 0.44 | 7.0 | 105/72 |
| †† | 1 ml. hog extr., 2 mg. desoxycorticosterone acetate per day | 9 | Overtreatment | 6.71 | 3.44 | 51.1 | 0.42 | 6.3 | 1.15 | 17.1 | 1.21 | 18.2 | 0.49 | 7.3 | 102/70 |
| 8‡‡ | Desoxycorticosterone acetate pellets | 31 | Fair maint. | 6.37 | 3.29 | 51.6 | 0.54 | 8.5 | 0.91 | 14.3 | 0.91 | 14.3 | 0.67 | 10.5 | 155/100 |
| §§ | Desoxycorticosterone acetate pellets, 5 ml. adrenal extr. per day | 4 | Good maint. | 6.24 | 3.12 | 50.0 | 0.43 | 6.9 | 1.06 | 17.0 | 1.06 | 17.0 | 0.57 | 9.1 | 140/90 |
| 9 | Desoxycorticosterone acetate pellets, nearly exhausted in 46 weeks | 46 | Slight insuffi. | 6.28 | 3.45 | 55.0 | 0.43 | 6.8 | 0.71 | 11.3 | 1.19 | 18.9 | 0.50 | 8.0 | 98/70 |
| | 1 ml. hog extr. per day, containing 2 mg. desoxycorticosterone acetate | 8 | Excellent maint. | 6.02 | 3.40 | 56.5 | 0.34 | 5.7 | 0.72 | 11.9 | 1.20 | 19.9 | 0.36 | 6.0 | 145/96 |

* Intermittent nausea.
† Pulmonary tuberculosis, probably arrested.
‡ Serum.
§ Appetite "keen."

** Face and eyelids puffy.
†† 90 gm. protein per day, 5 weeks.
‡‡ Weakness, headaches.
§§ Intermittent headaches, weakness decreased.

TABLE 3.—TISELIUS PLASMA PROTEIN DISTRIBUTION IN TREATED ADDISON'S PATIENTS.

| Case No. | Treatment | Period treated (wks.) | Maintenance | Total protein (gm./ 100 ml.) | Albumin | | α-globulin | | β-globulin | | γ-globulin | | Fibrinogen | | Blood pressure |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Gm./ 100 ml. | % total protein | Gm./ 100 ml. | % total protein | Gm./ 100 ml. | % total protein | Gm./ 100 ml. | % total protein | Gm./ 100 ml. | % total protein | |
| 11 | Desoxycorticosterone acetate pellets | 190 | Very good maint. | 5.80 | 3.43 | 59.2 | 0.49 | 8.5 | 0.79 | 13.6 | 0.64 | 11.0 | 0.45 | 7.7 | 105/75 |
| 12 | Desoxycorticosterone acetate pellets | 104 | Excellent maint. | 6.16 | 3.74 | 60.6 | 0.44 | 7.1 | 0.89 | 14.6 | 0.80 | 13.0 | 0.29 | 4.7 | 124/82 |
| 13 | Desoxycorticosterone acetate pellets | 85 | Good maint. | 6.54 | 3.67 | 56.1 | 0.37 | 5.7 | 1.10 | 16.8 | 1.06 | 16.2 | 0.34 | 5.2 | 100/70 |
| 14 | Desoxycorticosterone acetate pellets | 16 | Good maint. | 6.80 | 2.74 | 40.3 | 1.10 | 16.2 | 0.78 | 11.4 | 1.34 | 19.7 | 0.84 | 12.4 | 96/50 |
| 15* | 1 ml. hog adrenal extr. containing 2 mg. desoxycorticosterone acetate daily | 3 | Good maint. | 6.47 | 3.35 | 51.8 | 0.43 | 6.7 | 1.20 | 18.5 | 0.96 | 14.8 | 0.53 | 8.2 | 106/72 |
| 16 | 2.5 mg. desoxycorticosterone acetate, 5 ml. adrenal extr. per day | 12 | Good maint. | 5.37 | 3.11 | 57.8 | 0.43 | 8.1 | 0.70 | 13.1 | 0.78 | 14.5 | 0.35 | 6.5 | 118/70 |
| 17 | 2 ml. adrenal extr. per day | 6 | Good maint. | 6.03 | 3.08 | 51.0 | 0.45 | 7.4 | 0.78 | 12.9 | 1.07 | 17.9 | 0.65 | 10.8 | 106/80 |
| 18† | 5 mg. desoxycorticosterone acetate per day | 1 | Sl. overtreated | 5.53 | 2.65 | 47.8 | 0.58 | 10.5 | 0.93 | 16.8 | 0.91 | 16.1 | 0.46 | 8.3 | 100/66 |
| 19 | 85 ml. adrenal extract, 18 mg. desoxycorticosterone acetate in 6 days after extreme insuffi. | 1 | Improvement | 4.57 | 2.26 | 49.5 | 0.51 | 11.2 | 0.88 | 19.2 | 0.49 | 10.7 | 0.43 | 9.4 | 80/60 |

* Complicated by severe muscular contractions especially of knees and elbows.
† Slight edema.

hematocrit determinations only is not entirely valid, but it is believed that during recovery from adrenal insufficiency a good estimate of changes in plasma volume in an individual is probably obtained. Studies on adrenalectomized animals indicated the validity of this conclusion. In adrenalectomized dogs in which the dye method of estimating plasma volume was employed, "the importance of the change in plasma volume in modifying the red blood cell count and hemoglobin value is clearly shown by the blood volume decrease."[4] By frequent injections of adrenal extract and administration of desoxycorticosterone acetate in oil a constant supply of hormone was assured the patient at all times.

**Summary.** In the estimation of plasma proteins in 19 patients with Addison's disease, the Tiselius electrophoresis method was used for determination of the various protein fractions. When the patient showed definite signs of adrenal insufficiency, the total protein was usually in the upper normal range, and in all cases the albumin percentage of the total protein was definitely decreased. The increase in globulin was not consistent in any one fraction or fractions. All globulin fractions usually showed some increase.

After adequate maintenance with desoxycorticosterone acetate for a period of months, the albumin increased somewhat but did not return to normal. When large amounts of adrenal extract were used for a month or longer, further improvement was observed, and in some instances a normal or nearly normal protein distribution was attained.

We are greatly indebted to Dr. G. F. Cartland and Dr. Dwight Ingle of the Upjohn Company and Dr. David Klein of the Wilson Company for the adrenal extract used in these studies.

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## THE INCIDENCE, CAUSES AND INTERMITTENCY OF PROTEINURIA IN YOUNG MEN

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This paper reports a study of proteinuria in men being mobilized for war service, designed to answer certain questions: (1) What evidence lies behind the modern view that in the absence of associated

disturbances intermittent proteinuria of young persons is inconsequential and benign? (2) What is the incidence and nature of proteinuria in American men of supposed good health? (3) Does measurement of the concentration of protein assist in tracing the etiology of the proteinuria? (4) How effective is one urine analysis for recognizing and differentiating between nephritis, urologic disease and intermittent proteinuria?

Although by special methods trace amounts of mucins can be demonstrated in every normal or "negative" urine,[31,39] the tests for proteinuria as ordinarily performed detect albumins and globulins only.[6] In clinical proteinuria the proteins are identical in physical and immunologic properties with those of the blood,[3,7,14,27] but not the same nor as uniform in fractional distribution. When present, such urine proteins are referred to by tradition as "albumin," yet globulins are almost always present also, especially in nephritis and nephrosis. The term "proteinuria" is more exact and is to be preferred.

**The Benign Nature of Intermittent Proteinuria.** From the standpoint of the urine analysis itself, apart from clinical history and physical examination, intermittent or *orthostatic* proteinuria differs from nephritic proteinuria in two fundamental respects. Firstly with all varieties of nephritis—acute or chronic, glomerular, arteriosclerotic or pyelonephritic—the excretion of protein is almost always constant, regardless of posture or exercise.[18,21] The sole exceptions to this rule seem to be those occasional patients with mild chronic glomerulonephritis which remains subclinical and asymptomatic for years, and those convalescent from acute nephritis, when nearly well. In such types of cases the proteinuria may be absent or very slight when the individual is resting, but usually reappears during physical activity or on assumption of the lordotic position. Sometimes, too, a momentary clearing of a mild nephritic proteinuria can be effected during the forcing of fluids or by feeding alkali in large doses.[6,9,35] Secondly, nephritis invariably gives rise to erythrocytes and casts in the urinary sediment[6]; without this finding the diagnosis cannot be made. Even the exceptional mild or latent patients in whom the proteinuria is no longer constant usually excrete an increased number of red cells and casts, detectable by careful microscopy of fresh specimens or by quantitative procedures such as the Addis sediment count.[1] Thus, intermittent proteinuria (referring to the disorder, not the mere finding) is viewed by definition and custom as a urinary dysfunction distinct from true nephritis.

At times it is not easy to differentiate between the pure form of intermittent proteinuria and that which occurs in association with urologic disorders. It was noted in the series of trainees discussed later in this paper that proteinuria of extrarenal origin when present at all was more often discontinuous than regular. Rytand[37] has described 2 patients with urinary anomalies, who had clear negative urine when lying down, but on standing showed proteinuria associated with impaired diodrast excretion and the outpouring of casts, erythrocytes and renal epithelial cells. Young *et al.*,[41] and Prince[36] have advised an

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exhaustive investigation of every patient with proteinuria, to include along with the history and urine studies, the establishment of "normal kidney function (phthalein, urea clearance and dilution and concentration tests); normal blood chemistry, non-protein nitrogen, blood urea, total protein and albumin-globulin ratio; and negative plain Roentgen rays and normal intravenous urograms." However, the wide prevalence of proteinuria makes the practical carrying out of such a detailed diagnostic program economically unfeasible.

*One major reason for holding intermittent uncomplicated proteinuria to be benign* is its high rate of occurrence in groups of individuals otherwise normal, as compared with the relative rarity of kidney diseases in the same populations. Thus MacLean,[29] during the first World War on studying 50,000 British soldiers with salicylic acid reagent, found that 5.6% had proteinuria, in a single test. After deduction of specimens containing pus or spermatozoa and those with "less than 5 mg. per 100 cc." the more significant figure of 2.2% was secured.

Of 7041 French and British troops examined by McLeod and Ameuille,[30] in 1916, for proteinuria with the single specimen method, 263 positives (3.7%) were encountered.

Of 2269 cadets and officers at West Point Military Academy studied by Ashburn,[2] between 1925 through 1927, 360 (almost 16%) had proteinuria (quantities not stated), two-thirds of the cases being encountered in a single year. Of these, proteinuria was present once in 80%, twice in 16%, and more than twice in but 4%. Among 64 cadets showing protein at more than one examination, in 10 instances positive results were separated by a negative one. In 1 cadet the condition continued for 4 years and then cleared.

The incidence in 20,000 freshmen at the University of Minnesota, using the nitric acid ring test, was studied by Diehl and McKinlay;[18] 1065 (5.32%) had protein on the first examination, in amounts ranging from a trace (1+) in 841 to a heavy cloud (3 or 4+) in 64. On reexamination approximately three-fourths of those with a trace on entrance had become free, whereas of those with a heavy cloud, only 6% had become free. The authors found, on comparing 455 proteinuric students with 480 protein-free controls, that the first group was "but little inferior physically" to the second.

Using the heat and acetic acid test, Burden[11] studied a group of 3642 students entering the University of Pennsylvania: 949 (26%) had proteinuria; 69.3% were positive on the first examination only; 6.4% (61 cases) were tested for orthostatic changes, with positive results in 26.

Of 4500 Viennese youths aged 14 to 17 examined by Nowak,[33] 26 (0.8%) were stated to have nephritic proteinuria, and 524 (11.6%), the intermittent type, though criteria and methods were not given. Nowak was unable to demonstrate any relationship between lordosis and proteinuria. There were 2 unusual cases who excreted proteinuria persistently, day and night, on repeated examinations, and never any sedimentary changes of nephritis; both had some kyphoscoliosis and were placed in the non-nephritic group. Another boy, 14 years old,

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diagnosed at the first examination as orthostatic proteinuria, had persistent albuminuria and cellular elements of nephritis a year later, with no known episode of acute nephritis intervening.

After 25 years Bashford[4] reëxamined some 30 men who had had proteinuria when 14 to 16 years of age. All were in good health; only 1 still had protein in the urine. There was 1 other case, a man who had died 7 years after the initial examination, of "acute nephritis."

Blatherwick[10] reported on the urine findings in 15,000 employees of the Metropolitan Life Insurance Company (Kingsbury-Clark method), a group representative of the general population as regards age and sex distribution and state of health: 91.6% were negative, 3.3% had 10 mg. of protein, and only 1.7% had 20 mg. or higher.

In 1941, Lyall[28] reported on 20,000 men examined during recruitment for the British Armed Services, using the Esbach test: 110 (0.55%) had proteinuria. Of these, 31 exhibited no other findings; 22 were classed as *persistent albuminuria* without evidence of nephritis, though 9 had hypertension or transitory hematuria; 14 men were classed as *subacute nephritis*, 31 as *chronic* or *sclerotic nephritis* and in 12 the source of the protein was distal to the kidney, in renal stone, cystitis, or urinary tract infection.

In 1944, Murphy[32] reported that of 9994 men between the ages of 17 and 50 applying for enrollment in the U. S. Navy, the incidence of proteinuria was 3%; 85% were designated as orthostatic, 13.7% as pathologic and 1.3% as undetermined in type. Orthostatic proteinuria occurred almost exclusively in the younger age groups, being 5.1% in the 4517 who were 17 years old; no cases were discovered in men over 32. A seasonal variation was described, the highest incidence being in the summer months. "Postural defects were common, true lordosis or the lordotic posture being present in over 80% of the cases."

Another reason for giving a good prognosis to intermittent proteinuria is the rapid decline in its frequency with increasing age beyond adolescence. In Harvard freshmen of an average age of 18, proteinuria occurred in about 5%, according to Lee,[26] whereas in upper classmen, with an average age of 20, the incidence was but 3.5%. Diehl and McKinlay's[18] college freshmen were 5.32% positive, whereas MacLean's[29] group of soldiers, older in age, gave but 2.2% positive specimens. In Thorpe and Wakefield's[38] 100 Mayo Clinic patients with age range 4 to 47 years, 26 were 12 years or less, 67 were between 12 and 30, and only 7 were 30 or over. The average age was 18 years. In 64 cases of orthostatic proteinuria collected by Young, Haines and Prince[41] from the Johns Hopkins Hospital files, the ages ranged from 9 to 39 years, most being between 14 and 18 years.

Still another reason is the experience of actual follow-up studies on individual patients. Palmer[34] tracked down 35 former college students who with the nitric acid ring test had once had proteinuria. After 8 or more years but 2 still had traces of protein in the urine. Of 35 others replying to a questionnaire 10 years after the original finding, none had symptoms of renal disease.

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When Thorpe and Wakefield[38] reëxamined 64 orthostatic cases after an average interval of 7 years, all but 1 were in good health. Of 18 cases that had had persistent proteinuria with an orthostatic increase, only 2 showed renal disease an average of 7.7 years later; the urine of the remaining 16 had become entirely negative. Nor did any of Lee's[26] students with proteinuria develop nephritis over a 5-year observation period. Of 14 orthostatic patients followed by Young *et al.*,[41] 4 were protein-free after 2 years, 6 after 3 years, 1 after 6 years, and 3, 12 years later.

Evers,[20] in 1935, reported that insurees of the New York Life Insurance Company who had had proteinuria without casts or other evidences of nephritis, after 9 years showed no increase in mortality above normal expected levels. Similarly, Christiernin, Dublin and Marks,[13] in a survey of policies issued by the Metropolitan Life Insurance Company from 1925 to 1935, and studied in 1937 and 1938, found no unusual mortality in otherwise normal proteinuric individuals, although when the proteinuria had been associated with hypertension or obesity the mortality was much above normal expectation.

The figures for these large groups of normal individuals are not strictly comparable with each other, nor with the data which follow. The populations studied have not been identical from the standpoints of race, locality, or age and sex distribution, and techniques of testing and criteria taken to delimit proteinous from normal urine have been far from uniform. Only Ashburn, Burden and Murphy endeavored to carry out specific postural studies. The reports emphasize, nevertheless, that uncomplicated proteinuria occurs much more frequently than does nephritis or other forms of kidney disease, and that it is primarily a transitory disturbance of youth.

Thus, without denying that some individuals with intermittent proteinuria may have diminished renal function when standing in the lordotic posture,[40] it seems clear that any "injury" of the kidney responsible for such proteinuria is minor and transitory and quickly recovered from. An essential distinction exists between temporary reversible dysfunctions and more chronic continuing disease states. To generalize from the evidence now at hand, *when careful study reveals no signs of nephritis or urologic disease, particularly in a young subject, simple proteinuria of the intermittent type must be interpreted as a benign innocuous phenomenon.*

**Clinical Material and Methods.** The population group studied for proteinuria consisted of a consecutive series of 22,000 inductees received at the U. S. Maritime Service Training Station, Sheepshead Bay, N. Y., between Sept. 1, 1943, and June 1, 1944. These were fresh recruits drawn from all ranks and occupations of civil life. The majority came from the section of the United States bounded by the Rocky Mountains, Georgia and Canada. All were in supposedly good health on arrival, each enlistee having been examined and passed by Medical Officers in enrollment offices. Their ages ranged from 16 to 50 years. Two-thirds were below 26 years of age; approximately one-half were 20 years of younger (Table 1). Their urine specimens were

collected for analysis about 24 hours following arrival, after breakfast or in the early afternoon, on a day free from undue physical activity.

TABLE 1.—DISTRIBUTION OF 420 PROTEINURIA CASES
(1.9% of 22,000 Apparently Healthy Trainees)

| Classification | No. of cases | Distribution of 400 investigated cases (%) |
|---|---|---|
| Intermittent | 382 | 95.5 |
| Continuous | 7 | 1.8 |
| Nephritic | 8 | 2.0 |
| Urologic | 3 | 0.7 |
| Total completely studied | 400 | 100.0 |
| Study not completed | 20 | |
| Total | 420 | |

Preliminary screening for proteinuria was carried out with Robert's nitric acid-magnesium sulfate ring test. With this test a concentration of 25 to 30 mg. protein per 100 ml. of urine, read usually as "trace"* gives an opalescent ring of precipitated protein dense enough to be recognized without a black background. All protein-containing specimens positive at or above this threshold level were tested again with the Kingsbury-Clark[24] quantitative technique, in which turbidity produced by adding sulfosalicylic acid to urine is proportional to the quantity of protein present and can be measured against calibrated standards. This method is used by most insurance companies since it is peculiarly suitable for urines containing but small amounts of protein.[10]

Every man with proteinuria of 30 mg. or higher in the above initial examination was recalled. If later urines were negative further tests were not made, whereas if the proteinuria persisted for several successive specimens a 24-hour "orthostatic exercise" test was performed, as follows:

The bladder was emptied 1 hour after going to bed in the evening. Next morning, before rising, another urine specimen was secured. The subject then stook in the lordotic position for 30 to 45 minutes, leaning back at about a 135° angle. After voiding a third specimen, he went about the usual training routine. No fluids were taken during this day (no water, tea, coffee, soft drinks, milk, soup and so forth) in order to secure information on renal concentration power from the specific gravity determinations. All specimens passed through the day were collected and tested individually.

Subjects in whom proteinuria was present constantly even when lying down, or who exhibited abnormal sediments of red cells, leukocytes, or more than a few casts were admitted to the adjoining U. S. Public Health Service Hospital to be observed for nephritis or urinary tract lesions.

* Terms used in recording "urinary albumin" tests vary greatly in different laboratories. The scale of comparison recommended for the Army (Laboratory Methods of the United States Army, edited by J. S. Simmons and C. J. Gentzkow, Lea & Febiger, Philadelphia, 1944) reads as follows:

Faint trace (±), less than 10 mg. per 100 ml.; trace (+), 10 to 40 mg.
Small amount (++), 100 mg.; moderate amount (+++), 200 to 300 mg.; large amount (++++), more than 500 mg.

**Classification and Frequency of Proteinuria.** In the initial specimens, 420 of the 22,000 inductees (1.9%) gave urine protein concentrations of at least 30 mg. per 100 ml. Of these men, 20 were transferred or discharged from the Service before the studies could be completed. After diagnostic study the remaining 400 were classified as: (*a*) *intermittent* proteinuria, 382 instances, (*b*) *continuous* proteinuria without any associated changes, 7 instances, (*c*) *nephritic* proteinuria, 8 instances, and (*d*) *urologic* proteinuria, 3 instances (Table 1). The data are summarized in the ensuing paragraphs, along with discussions of nosologic criteria, age distributions, concentrations of urinary protein and noteworthy features encountered.

*Intermittent Proteinuria.* Under this heading have been placed 382 men whose urines were at times protein-containing and at other times protein-free. None of these had a history of antecedent nephritis; all showed normal sediment in the urine on repeated examinations and were free from hypertension and constitutional findings indicative of renal disease.

Of these, 192 had protein and gave one or more protein-free specimens after the first positive specimen. The urine protein concentrations varied from 30 mg. to 350 mg. per 100 ml., with a mean of 66 mg. 89 others had protein in 2 or more successive random specimens, and then gave negative tests thereafter; their range of protein concentration spread up to 400 mg. per 100 ml. with a mean of 70 mg. With a few of these men some transient irritative stimulus such as an acute infection or physical strain or the excitement accompanying the change from civil to barracks life may have evoked a brief period of proteinuria. With others albuminous fluid from seminal vesicles, prostate or urethra may have contaminated the urine transiently. With most, however, if not all, the proteinuria would undoubtedly have been found to be recurrent and remittent if they had been observed over a continuous 24 hour period, as were those described in the next paragraph.

The remaining 101, after passing 2 or more positive specimens, were subjected to the "orthostatic" exercise routine of study. Every one was found to exhibit proteinuria at least once during this 24 hour observation period. In 83 of these the proteinuria conformed in general with the accepted criteria for orthostatic albuminuria: When they were lying down the urine was protein-free; when upright or lordotic, proteinuria was constant or intermittent. In the other 18 the urine was protein-free during the daytime hours, but contained small amounts of protein in the night urine, with a definite rise after taking the lordotic exercise. Of the whole group, 6 had intermittent excretion of protein in one 24 hour period, but some days later when the test was repeated gave an entirely negative series of specimens.

The concentrations of protein in the urine of these 101 men varied widely, the values for single specimens ranging from 10 to 3000 mg. per 100 ml. urine. The *averages* for the protein-containing specimens of each subject per 24 hours had extremes of 15 and 545 mg., and a grand mean of 74 mg. per 100 ml. Nine individuals produced single specimens containing more than 200 mg. of protein per 100 ml.

The above figures were gathered while the fluid intake was restricted as recommended by Derow.[16] Every subject was able to excrete urine of high specific gravity, showing that the concentrating power of such proteinuric kidneys was not impaired to any extent. The range for the individual maximum specific gravity figures was 1.025 to 1.034, with a mean of 1.029.

These 382 subjects seemed to possess the clinical variety of proteinuria best called intermittent, though known also as physiologic, periodic, postural, orthostatic, orthotic, lordotic, cyclic, juvenile and so forth.[12,23,25,36,41] The condition is fairly common during childhood, attains maximum incidence in adolescence and then declines in frequency as adult maturity is reached.[23] The present series (Table 2) demonstrates the latter half of this cycle. At 16 years of age the incidence was highest, 4.6%; at 17 years, it became 3.08%; at 18, it was down to 1.61%.

TABLE 2.—THE AGE FACTOR AS RELATED TO PROTEINURIA (400 CASES)

| Age (yrs.) | No. of trainees | Intermittent | | Continuous | Nephritic | Urologic | Total | |
|---|---|---|---|---|---|---|---|---|
| | | No. | % of age group | | | | No. | % of age group |
| 16–20 | 11,822 | 300 | 2.54 | 1 | 4 | 3 | 308 | 2.61 |
| 16 | 2632 | 121 | 4.60 | | 1 | | 122 | 4.64 |
| 17 | 1948 | 60 | 2.08 | | 1 | 1 | 62 | 3.18 |
| 18 | 5208 | 95 | 1.61 | 1 | 2 | 2 | 100 | 1.92 |
| 19 | 1167 | 16 | 1.37 | | | | 16 | 1.37 |
| 20 | 867 | 8 | 0.92 | | | | 8 | 0.92 |
| 21–25 | 3,719 | 27 | 0.73 | 1 | 3 | | 31 | 0.83 |
| 26–30 | 3,798 | 28 | 0.74 | 3 | | | 31 | 0.82 |
| 31–35 | 2,127 | 17 | 0.80 | 2 | | | 19 | 0.89 |
| Over 35 | 534 | 10 | 1.87 | | 1 | | 11 | 2.06 |
| Totals | 22,000 | 382 | 1.74 | 7 | 8 | 3 | 400 | 1.82 |

None of these subjects had undernutrition or a skeletal deformity, and all had satisfactorily passed the thorough physical examination required for entry into the Maritime Service. The Station orthopedist* compared the habitual position of the spine in a series of 100 intermittent proteinuric trainees with an equal number of non-proteinuric trainees, and failed to uncover any differences between the two groups in the incidence of lordosis and other postural faults. The amount of lordosis of the lumbar spine was determined clinically by means of inspection and palpation, using arbitrary symbols 1+, 2+ and so forth as criteria of comparison. The data when tabulated were as follows:

| Amount of lordosis of lumbar spine: | 0 | 1+ | 2+ | 3+ | 4+ | Total |
|---|---|---|---|---|---|---|
| Controls | 46 | 31 | 15 | 6 | 2 | 100 |
| Intermittent proteinuria | 41 | 26 | 19 | 12 | 2 | 100 |

Thus the control group had 54% with lordosis and the proteinuria group had 59% with lordosis. When rearranged into groups according to severity of lordosis, no significant difference was evident between the proteinurics and the controls. These observations do not controvert

* Dr. Renato Ricca, Asst. Surgeon, U. S. Public Health Service (Reserve).

the well-established pathogenetic relationship which can exist between lordosis and proteinuria—indeed, most of the present group of cases excreted more protein when placed temporarily in the lordotic position. Instead, they demonstrate that with non-lordotic individuals other factors can excite escape of protein into the urine.

For the reasons given in the preliminary discussion all inductees having such uncomplicated intermittent proteinuria were permitted to proceed in training without restriction.

In passing, it is of interest to record that with many men who exhibited proteinuria during and immediately after the "orthostatic exercise," the clearing of the voided specimens took place gradually and stepwise when they were made to lie down after spending 30 to 45 minutes in the lordotic position. In successive specimens collected at 30 minute intervals traces of protein were in a few instances still present after 3 hours. This lag in disappearance of the protein was probably due to incomplete emptying of the bladder during voiding, permitting some of the earlier lordotic urine to remain and mix with later recumbent urine flowing in from the ureters. The factor of incomplete bladder emptying was not considered in a recent recommendation[17] for quick differentiation of albuminuric Army inductees by collection of but 2 specimens, 1 immediately after lordotic exercise, the second, ½ hour later.

Murphy[32] very recently has reported that proteinuria in his series of Navy applicants was more frequent in July and August than later in the year. To check his observation this Station's figures for the months of June through September 1944 were reviewed. The frequency of proteinuria for all new trainees, expressed in round numbers, was as follows: June, 2.6%; July, 5.2%; August, 6%; September, 3.5%. The distribution of the new trainees as regards the age factor was approximately the same for each of these months. It did not seem wise to draw conclusions for earlier than June, inasmuch as the Station, prior to that month, had not taken in men under 18 years of age in appreciable numbers, whereas from June 1 onward nearly 75% of the inductees were younger than 18 years. These limited data, so far as they go, substantiate Murphy's finding. The phenomenon of seasonal variation seems not to have been reported heretofore; no doubt it is related in some way to the almost universal production of urine of high specific gravity and reduced volume during the heat of the summer.

*Continuous Proteinuria.* Seven men had protein in all specimens collected. Five were 25 to 27 years of age, 1 was 18 and 1 was 31. Two were moderately overweight; the others were slender. None gave a history of antecedent nephritis. One had a weak positive serology titer for syphilis, without any clinical signs of the disease. One patient, aged 26 years, when subjected to 5 separate 24 hour "orthostatic" studies had protein in all but 2 sporadic specimens collected on different afternoons. Another patient's proteinuria had been first recognized 7 years earlier. Blood pressures and other findings were normal in all. In single specimens the range of protein

extended from a minimum concentration of 10 mg. to a maximum of 600 mg. per 100 ml. Recumbent values were not much lower than those during activity. The mean figures for all the tests on each individual were, in increasing order, 45 mg., 51 mg., 51 mg., 56 mg., 81 mg., 216 mg., 250 mg.* A few white cells and hyalin casts were found sporadically in the urine of each. On concentration tests, 4 produced urines of 1.030 specific gravity, 1 attained 1.025, 1 was 1.021 and 1 was not tested. Renal function tests showed no noteworthy impairment. Addis sediment counts done repeatedly on the urines of 5 of the 7 proved normal in every instance. Intravenous pyelograms performed on 5 showed normal uteropelvic patterns.

Because of the suggestion[6,9,35] that alkalinization of the urine may clear the urine in functional but not in nephritic proteinuria, sodium bicarbonate was administered to 2 subjects. Their proteinuria ceased temporarily to recur as soon as alkalinization was stopped. Enough exceptions occur both ways[18,21] to negate the value of this phenomenon as a diagnostic test.

Since these 7 men with continuous proteinuria showed no indications of renal dysfunction apart from the proteinuria, and since there were no other data to connote antecedent nephritis or latent chronic renal disease, they were permitted to proceed with training and to go out to sea on merchant vessels. Inasmuch as recruits remain at this station but a relatively short time—1 to 5 months—no opportunity exists for observation of the ultimate outcome of their proteinuria. Murphy[32] found 4 apparently similar instances among 9994 Navy recruits. These were all 17 years of age; displayed proteinuria not affected by postural changes; and had no other noteworthy features.

No evidence was encountered to suggest that kidneys which leak protein are unusually susceptible to the toxic agents that induce glomerulonephritis. MacLean[29] had found the distribution of "trench nephritis" to be no higher among troops who had exhibited a positive protein test earlier in the campaigns than among those whose urines had been negative. A similar generalization may be drawn from the present study. Of 27 cases of acute glomerulonephritis and 7 cases of acute pyuria which developed among the 22,000 recruits subsequent to entry on the Station, not one single instance came from the group of 420 individuals who had manifested proteinuria in the initial arrival urinalysis.

*Nephritic Proteinuria.* The diagnosis of mild or latent nephritis was made in 8 instances. All had mild hematuria and abnormal quantities of red cells and casts in Addis counts. All showed protein in every specimen examined, including those collected while recumbent. Several had diminished phenolsulphonephthalein excretion, slight elevations of blood pressure, and other evidences of impaired renal function. In age, 7 were between 16 and 24 years; the eighth was 37 years old. The concentration of urinary protein per 100 ml. in their admission specimens were, respectively, 30 mg., 40 mg., 75 mg., 200 mg., 200 mg., 280 mg., 375 mg., 725 mg.

On physical examination these subjects did not appear ill and were

*See footnote, page 91.

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unaware of the existence of the renal lesions. Diagnosis of the exact kind of nephritis was not feasible in view of the absence of opportunity for long-range follow-up of their progress. However, these men were all given discharges from the Maritime Service by the Medical Board because of the probable chronic nature of the condition and the possibility of serious complications which might interfere with training and later sea duty.

*Urologic Proteinuria.* Three disturbances in the realm of urology were uncovered by the initial urine examination. There was 1 case of acute cystitis and 1 of gonorrheal urethritis, both of which cleared under treatment; and 1 case of hydronephrosis which was discharged from the Service. With each of these the entrance urine specimen contained but a trace of protein, 30 mg. per 100 ml.

*In Summary.* Of a total of 400 recruits studied for proteinuria, 382 had the benign intermittent type and 7 the continuous type, probably benign; 8 had asymptomatic nephritis; 3 had urologic disturbances. Only the 7 nephritis cases and 1 urologic case were discharged from the Service; with the remaining 392 (98%), the proteinuria was adjudged no handicap to training. The other 20 men in the full series of 420 were not adequately studied.

**Concentration of Protein in the Urine.** It is, of course, well known that nephrotic patients and those ill with acute or severe nephritis may show high concentrations of urinary protein, from 1 to 5 gm. per 100 ml., or higher. However, as already discussed, in the milder forms of organic renal disease the levels may be lower, and usually are, ranging down to complete absence of protein when the subject is recumbent. The protein then appears only with change from the resting position.

Physicians often inquire whether one can utilize the information concerning the amount of protein in one random sample of urine as an aid in diagnosis. Since the present group of cases is apparently the first large series in which the protein content of single specimens has been scored in direct quantitative measurements rather than by the crude and confusing "number-plus" system, it is of interest to review the data from this standpoint. The findings are tabulated in Table 3, along with the ranges and mean concentrations of protein as encountered in continuous, nephritic and urologic proteinuria. The 3 urologic cases had a mean of 30 mg. per 100 ml.; the intermittent cases, 70 mg. per 100 ml.; the continuous cases, 107 mg.; and the chronic nephritis cases (admission urine) 240 mg.

TABLE 3.—CONCENTRATION OF PROTEIN IN URINE WITH DIFFERENT TYPES OF PROTEINURIA

| Classification | No. of cases | Observed range of individual specimens (mg. per 100 ml.) | Mean (mg. per 100 ml.) |
|---|---|---|---|
| Intermittent | 382 | 10–3000 | 70 |
| Continuous | 7 | 10– 600 | 107 |
| Nephritic (initial specimens) | 8 | 30– 720 | 240 |
| Urologic | 3 | 30– 30 | 30 |

Thus the magnitude of the concentration of protein in a single specimen of urine is unreliable as a major criterion for distinguishing among

the various types of proteinuria. Indeed, the specimen richest in protein encountered in this study (3000 mg. per 100 ml.) came from a 19 year old with inconstant proteinuria, whereas 3 of the 7 cases of nephritis had protein concentrations on admission which were as low or lower than the grand mean value for the intermittent group of cases. Viewed statistically, however, the most serious disturbance had the highest average value.

In chronic nephritis, Berglund, Scriver and Medes[6,9,35] noted the *rate* of protein excretion to be independent of fluid intake and output, urine specific gravity or urine protein concentration, though a temporary increase may follow a change from rest to active walking, or a more permanent rise accompany the change from a low to a high protein diet. In other words, under constant conditions of physical activity the protein excretion per hour remained about the same regardless of whether there was a diuresis or a highly concentrated oliguria. Hence it is not possible to estimate the total daily excretion of protein from the amount in a single urine sample, unless the rate of urine secretion is known also. In acute nephritis, on the other hand, Berglund and Frisk[5] and Bing[7] have noted that the proteinuria is subject to quick inexplicable changes, irrespective of diet, particularly in the direction of improvement.

Many life insurance firms[15] now no longer refuse policies to prospective policyholders who are in good health apart from small quantities of protein in the urine. The threshold level has been set at about 50 to 75 mg. of protein per 100 ml. of urine to delimit "harmless" from "suspicious" proteinuria, the precise figure varying with different companies. The errors inherent in the use of such arbitrary limits are obvious from the preceding discussion: many subjects with benign intermittent proteinuria come above these values, occasional mild nephritis cases produce protein concentrations below 50 mg. per 100 ml., and by rest, forcing fluids and ingestion of alkali a canny applicant can temporarily reduce a moderate albuminuria of whatever etiology to a low level or make it disappear altogether.

**Reliability of One Urine Analysis for the Detection of Proteinuric Disorders.** A so-called routine urinalysis is an essential component of any good physical examination. One purpose of this test is to detect manifestations of renal disease and related disorders.

The records of the 22,000 trainees have been scrutinized to ascertain the trustworthiness of a single urine examination as a screen for the detection of nephritis, urologic disorders, and benign proteinuria.

*Nephritis.* The routine admission urine analyses brought to light 8 cases of nephritis, all mild, symptom-free and unsuspected. During the subsequent 1 to 5 months that the 22,000 recruits remained on the Station for training, not another instance of preëxisting nephritis came to the notice of the medical staff even though at one time or another nearly every man had occasion to seek medical service either in his barracks sick-bay or at the base hospital. Mention has already been made of the 27 men who became ill with acute postinfectious glomerulonephritis during their training; not one showed protein in the original urine specimen collected on arrival.

Inasmuch as protein escapes almost continually into the urine during nephritis, any one urinalysis carefully done should reveal its presence. Only when a patient has nearly recovered from an acute attack or is in a subclinical phase of long-standing chronic glomerulonephritis does the proteinuria of nephritis become irregular and inconstant; in those exceptional cases erythrocytes and casts in the sediment are present to indicate the diagnosis.

*Urologic Disturbances.* Only 3 such cases were caught by the initial screening test. Later, during training, 17 other subjects came forward with major urinary tract disorders which must have been existent on arrival, though their initial examinations were negative. Three of these had infected hydronephrosis, 5 had major anomalies of one kidney, usually with associated infection, 4 had disturbances of the ureters or bladder, and 5 had renal calculi. Most of the infection cases had to be discharged and sent home. Thus it is obvious that urologic lesions will often be missed if reliance is placed on a single urine examination.

*Benign Proteinuria.* Of the 22,000 men, 1.8% exhibited benign proteinuria in the initial specimen. 2.5% were 18 years old or younger, and the age factor played a significant rôle. Some had exhibited but 1 positive specimen followed by 1 or more negatives, whereas others had shown 2 or more proteinous specimens before negative ones were secured. It was noted further that the intermittency or inconstancy of the proteinuria is one cardinal urinologic difference between this kind of proteinuria and active nephritis. The question naturally arises, how often would this fluctuant disturbance escape detection in a single routine urinalysis?

To get a truer picture of the frequency of proteinuria in healthy men, a more intensive study* was carried out on a group of 110 trainees. Over a 5 day period 8 separate urine specimens were collected from each, at noon and late afternoon for 3 days, and then on the following days at noon. During this experiment the men were physically active, occupied with drill, swimming and busy work assignments. Sixty-six were 16 years old; the age distribution of the remainder paralleled roughly that of the basic population of 22,000. *Not one had had protein in the initial specimen collected at the beginning of training.*

Tabulation of the 8 analyses yielded an unexpected high frequency of proteinuria. Of the 110 men, 62 (56%) produced at least 1 protein-containing specimen, and 14 (13%) had protein in more than half of the specimens collected. The exact figures were:

| Positive | Negative | Instances |
|---|---|---|
| 8 | 0 | 2 |
| 7 | 1 | 3 |
| 6 | 2 | 2 |
| 5 | 3 | 7 |
| 4 | 4 | 11 |
| 3 | 5 | 7 |
| 2 | 6 | 9 |
| 1 | 7 | 21 |
| 0 | 8 | 48 |

* These determinations were done with the photo-electric colorimeter, which adapts itself most efficiently to the measurement of precipitation turbidity.

The occurrence of positive tests was not significantly higher for the 16 year old fraction of the group than for the more mature trainees. The highest protein-containing specimen had a concentration of 328 mg. per 100 ml. and there were 9 others over 100 mg. per ml. However, the great majority of the readings fell in the 20 mg. to 60 mg. zone, the over-all mean being 52 mg. per 100 ml. The bulk of the readings thus corresponded to *1+* in the semiquantitative code for recording protein in urine. The microscopic examinations were all negative. Typhoid vaccine inoculations received in the middle of the week of study did not evoke a wave of proteinuria.

Thus, if 62 of 110 men, even though the majority are youthful, will display proteinuria once or oftener when studied with multiple urinalyses, then obviously intermittent proteinuria is much more prevalent in the general population than indicated by text-book statistics compiled from random single tests.

To conclude, *a random urine specimen can be depended upon nearly always to bring to light active nephritis if present, since in this disease, save in a few exceptional phases, protein and pathologic sediments are being excreted constantly day and night into the urine. In contrast, chronic urologic disturbances and benign intermittent proteinuria are subject to frequent intermissions. To establish their presence or absence one needs a fair number of specimens collected during different stages of physical activity.*

**Summary.** Urine examinations performed on 22,000 presumably healthy American men entering the U. S. Maritime Service revealed proteinuria in 420 (1.9%). In most instances, representing 1.7% of the original group, the proteinuria was intermittent or "orthostatic," with incidence highest at age 16.

The remaining cases in the series had either continuous proteinuria due to no elicitable cause, or mild unsuspected nephritis, or urologic disease.

Review of the cases and of the observations on record indicates that intermittent proteinuria in the age period covered is a harmless benign condition, provided there are no associated clinical or urinary changes.

In the study of disturbances accompanied by proteinuria, the concentration of protein in random specimens of urine is not helpful as a diagnostic guide.

In random urinalysis of single specimens nephritis will usually reveal itself. But more cases of urologic or benign intermittent proteinuria will be missed than caught.

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## ELECTROCARDIOGRAPHIC CHANGES ASSOCIATED WITH LESIONS IN THE DEEPER LAYERS OF THE MYOCARDIUM

### An Experimental Study*

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alone or the entire cardiac wall. Until recent years, no intensive study of the ECG effects of lesions confined to the deeper layers of the myocardium had been carried out, but recently efforts have been made to clarify this phase of electrocardiography.

Boyd and Scherf[2] (1940) in 17 experiments on dogs scarified the inner surface of the left ventricular apex with a sound introduced through the left auricle. No striking modifications in standard lead ECG's occurred after this procedure. The maximal effects were represented in a series of tracings in which there was a slight depression of the RS–T segment in Leads II and III and a reversal in the direction of the T wave in all 3 standard leads. Even these changes disappeared within 6 minutes.

Kisch, Nahum and Hoff[5] (1940), on the basis of experiments in which potassium chloride was applied to the surface or injected into the muscle layers of the hearts of dogs, cats and rabbits, suggested that "The magnitude of the ECG changes following injury to the heart is almost entirely conditioned by the nature, extent and location of the surface involvement. It is possible that the electrical activity of the ventricles is a phenomenon which is determined largely by the surface of the heart."

Robb and Robb[7,8] (1939) suggested that injury to a specific muscle bundle produces characteristic alterations in standard lead ECG's. Infarction of a specific muscle bundle has ECG consequences of a similar nature regardless of whether the injury to the muscle bundle involves its deep or superficial portion. These workers concluded that distribution of segmental elevation or depression among the standard lead tracings defines the muscle bundle which has been the site of injury.

On the basis of clinical observations, Master, Gubner, Dack and Jaffe[6] suggested that "myomalacia following coronary insufficiency differs as a rule from that following coronary occlusion by its focal and disseminated character and by its localization in the subendocardium and papillary muscles of the left ventricle" and that "the electrocardiogram of acute coronary insufficiency with infarction is characterized by the presence of a depressed RS–T segment and flattening or inversion of the T wave in 2 or more leads." And finally, "The presence of a depressed RS–T segment in acute coronary insufficiency is attributed to the subendocardial localization of the infarction."

For several years in articles on varying subjects, Wilson and associates[3,4,9–13] recorded observations on the contribution of the deeper layers of the myocardium to the ECG. Two of their conclusions follow: In direct leads from regions in which the inner layers of muscle were dead or had been replaced by scar tissue and in which the outer layers were still living and responding to the excitatory process, the QRS group was characterized by specific changes in that portion preceding and including the intrinsic deflection. The RS–T segment was not displaced. On the other hand, Wilson and associates observed that when a sharp electrode was thrust through the ventricular wall into the ventricular cavity, and thence into the subendocardial muscle

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of the dorsal wall of the heart, the resulting curves manifested essentially the same pronounced shifts of RS–T segment as occurred when the same type of electrode was introduced into the epicardial layers of the heart.

These several reports have no striking conformity. In 3 of them, the conclusion is that deep myocardial lesions produce either no change in the standard lead ECG or the minor and relatively non-specific alterations represented in slight depression of the RS–T segment and flattened or inverted T waves.

**Purpose of Study.** Our own attempt to define ECG changes that could be regarded as characteristic of lesions limited to the deeper layers of the myocardium was not undertaken in an effort to confirm or disprove any of the foregoing views. Rather, we wished to know whether large areas of myocardial damage could exist without ECG changes of a specific, constantly recurring type. If lesions of this kind occur, a likely site for them is in the subendocardial layers.

**Method.** *Traumatizing Instrument.* The difficulties of producing a lesion confined to the subendocardial myocardium are obvious. Although several methods were tried, an entirely satisfactory technique was not devised. The mechanical method finally was selected principally because it appeared to afford the only approach that permitted relatively exact localization of lesions. The method has apparent limitations, but if these are recognized the inherent error is not sufficiently great to invalidate the conclusions. Our original intention was to study the ECG effects of deep injuries in both the acute and chronic phases; however, experiments of long duration were abandoned because of limitations of the method.

The traumatizing instrument consisted of a piece of piano wire with a coil of one and a half loops at the end. The shaft of the wire was run through a Luer-Lok needle. To produce a lesion, the coiled portion of the traumatizing instrument was directed into the apical portion of the left ventricle, much as a corkscrew would be driven into a cork. At the conclusion of this initial stage the curved portion of the instrument lay free in the ventricular cavity. By altering slightly the direction of the shaft and allowing it to move through the hilt toward the ventricular cavity, fibers of the subendocardial myocardium could be caught in the revolving loops of the spiral. Gentle traction applied to the shaft usually produced tearing of the fibers enmeshed in the spiral. The greatest single difficulty, as a rule, was encountered on attempting to withdraw the traumatizing instrument. This hazard developed as a result of entanglement of partially severed strands of endocardium in the coils of the instrument. In most instances, little bleeding occurred after withdrawal of the wire and usually this was controlled readily by digital pressure over the bleeding point.

*Material.* Fifty-nine dogs varying in weight from 3 to 57 kg. were used. The majority of the experiments were performed on medium sized animals weighing between 10 and 20 kg. The fact that ECG's of dogs exhibit significant spontaneous variations from day to day is well recognized; however, such variations were not observed in experiments of a few hours duration in which the animals were maintained in a fixed position.

*Anesthetic Agent.* Anesthesia was induced with pentobarbital sodium administered intravenously; 25 mg. per kg. of body weight usually was adequate to induce anesthesia of sufficient degree for a surgical procedure. In order to maintain anesthesia, further pentobarbital sodium was given either intravenously or subcutaneously. That the

induction of anesthesia in dogs by use of pentobarbital sodium produced no significant changes in the ECG is indicated by the carefully controlled experiments of Betlach[1] and by our own experiments in which ECG's were made before and after anesthetization.

*Procedure.* The dog was laid on its right side. The thoracic cavity was entered by an incision through the sixth intercostal space. At this time artificial insufflation was instituted and maintained throughout the remainder of the experiment. A small opening was made in the apical pericardium, but an attempt always was made to maintain the major attachments of the pericardium so that the preoperative relationships of the heart were disturbed as little as possible.

An effort then was made to produce a deep lesion by using the spiral wire technique previously described. Usually the entire procedure was performed in 1 to 2 minutes. If it appeared unlikely that an adequate lesion had resulted from the first attempt, the entire procedure was repeated, usually about 1 hour after the initial attempt.

*Electrocardiograms.* With an ECG (Sanborn cardiette) so standardized that a current of 1 mv. produced a beam deflection of 1 cm., ECG's were taken at the following times: (1) after anesthesia, with the dog fixed in the position to be maintained throughout the remainder of the experiment; (2) after opening the chest and apical pericardium; (3) immediately after traumatizing the heart or carrying out any control procedure; and (4) at varying intervals thereafter.

**Results.** The results, which we regard as significant, were obtained only after use of precordial leads was begun. It is regrettable that in our earlier experiments records were obtained only with the standard leads. In the 59 experiments on dogs, at least 1 precordial ECG was obtained in 25. In this latter group, the exploring electrode was placed at one or at several positions over the precordium. In all cases in which any precordial lead was used, tracings were obtained with the exploring electrode over the cardiac apex and the indifferent electrode on the right foreleg. Connections were so made that a positive potential at the exploring electrode resulted in an upward deflection of the galvanometer beam. This apical lead is comparable, therefore, to the apical IV–R lead in human electrocardiography.

Of the 25 experiments in which at least 1 precordial ECG was obtained, all but 3 are included in this analysis. In 2 of those excluded, the cardiac lesions were small and the ECG changes were minimal. The results are represented adequately in the earlier phases of certain of the more satisfactory experiments in which the final lesion was achieved in 2 or 3 stages. The third experiment was discarded because the dog died before satisfactory ECG's could be obtained. With these exceptions, the following results are the product of 25 consecutive experiments.

*Changes in the QRS Complex.* Alterations of significant degree in the form of the QRS complex in the apical IV–R lead occurred in each of the 22 experiments (Table 1). Many of the following measurements were made on ECG's taken at or near the end of the experiment, sometimes several hours after final traumatizing procedures had been performed. These data, therefore, indicate trends of change rather than instantaneous developments.

TABLE 1.—CHANGES IN THE Q, R AND S WAVES AFTER DAMAGE TO THE DEEPER LAYERS OF THE MYOCARDIUM
(Apical IV–R Lead)

| Dog No. | Height of R wave (mm.) | | Depth of Q wave (mm.) | | Depth of S wave (mm.) | |
|---|---|---|---|---|---|---|
| | Pre-trauma | Post-trauma | Pre-trauma | Post-trauma | Pre-trauma | Post-trauma |
| 1 | 18 | 4 | 0 | 0 | 2 | 3 |
| 2 | 17 | 4 | 0 | 0–1 | 4 | 13 |
| 3 | 15 | <1 | 0 | 0 | 6 | 3 |
| 4 | 12 | 1 | 0 | 0 | 4 | 3 |
| 5 | 20 | 3 | 0 | 0 | 12 | 9 |
| 6 | 17 | 1 | 0 | 0 | 0 | 11 |
| 7 | 19 | 2 | 0 | 0 | 2 | 4 |
| 8 | 11 | 1 | 0 | 0 | 4 | 5 |
| 9 | 8 | <1 | 0 | 0 | 6 | 4 |
| 10 | 12 | 1 | 0 | 0 | 9 | 15 |
| 11 | 12 | 2 | 0 | 0 | 3 | 10 |
| 12 | 13 | 2 | 0 | 0 | 2 | 3 |
| 13 | 14 | 1 | 0 | 0 | 6 | 10 |
| 14 | 14 | 0 | 0 | 0 | 6 | 4 |
| 15 | 22 | 3 | 0 | 0 | 3 | 7 |
| 16 | 23 | 2 | 0 | 0 | 2 | 7 |
| 17 | 12 | 23 | 0 | 4 | 0 | 0 |
| 18 | 14 | 17 | 0 | 0 | 2 | 0 |
| 19 | 18 | 9 | 0 | 0 | 2 | 0 |
| 20 | 15 | 8 | 0 | 0 | 5 | 0 |
| 21 | 16 | 6 | 0 | 4 | <1 | 0 |
| 22 | 30 | 7 | 0 | 3 | 2 | 0 |

Diminution in the height of the R wave after infliction of deep trauma was the change most commonly noted (Figs. 1, 2, 3, 4 and 5). In no instance was the height of this wave before trauma less than 8 mm.; it averaged 15 mm. After myocardial injury, its height decreased to a level less than 4 mm. in 16 of the 22 experiments. In 10 of the 16 instances in which the R wave diminished in height, the S wave became deeper. In only 3 experiments was this increase in depth more than 5 mm. Concerning the other 6 of the 22 experiments, the R wave became shorter in 4 and higher in 2. In every instance in these 6 experiments the S wave disappeared completely and either a notch on the upstroke of the R wave or a Q deflection developed.

Significant widening of the QRS complex after infliction of deep trauma occurred in 2 experiments. In 1 instance (Figs. 6 and 7) this complex in control tracings measured 0.04 second and after trauma 0.08 second, and in the other, 0.05 second and 0.07 second, respectively.

Increased depth of the Q wave in Leads II and III occurred in 7 of the 22 experiments. The Q wave in the control tracings was absent in only 2 of these 7 instances. The greatest increase in depth was 5 mm. The significance of this alteration is reduced by the inconsistency of the presence and size of the Q wave in the control tracings and the relatively minor increase in the depth of this wave following trauma.

Changes in the form of the QRS complex in Lead I were noted frequently. However, the amplitude of the deflections in this lead were invariably small, significantly altered by respiratory movements, and consequently the changes were difficult to interpret.

*Changes in the RS–T Segment.* Significant elevation of the RS–T segment occurred in only 2 of the 22 experiments. In 1 of these, an

unusual amount of surface damage was present. In the other, the deep lesion extended close to the surface of the posterior wall of the left ventricle. However, in 34 earlier experiments not included in this survey, 3 instances of segmental elevation occurred. In at least 1 of these, no unusual degree of surface damage could be identified.

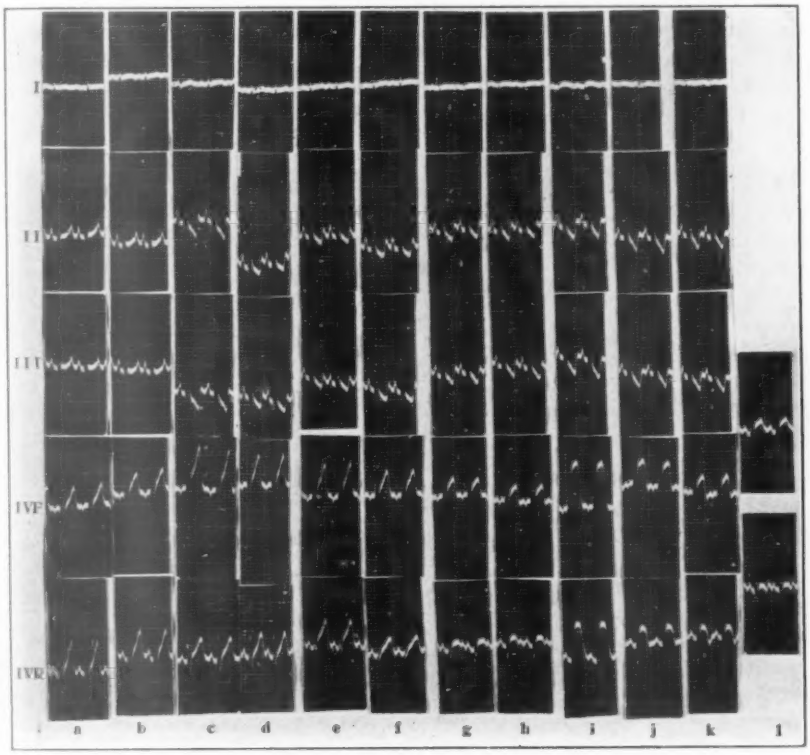


FIG. 1.—Dog 14. Roman numerals and capital letters represent the leads. *a*, Control after anesthesia; *b*, control after opening the chest and pericardium; *c*, 10 A.M., 5 min. after the first attempt at deep trauma (this lesion probably involved the posterior septum and the posterior papillary muscle); *d*, 10:35 A.M., 40 min. after the first attempt at deep trauma; *e*, 10:57 A.M., 5 min. after the second attempt at deep trauma (this lesion probably extended anteriorly across apical septum onto wall of apical portion of left ventricle anteriorly); *f*, 11:50 A.M., 58 min. after the second attempt at deep trauma; *g*, 1:45 P.M., 2 hrs. 50 min. after the second attempt at deep trauma; *h*, 3:15 P.M., 4 hrs. 25 min. after the second attempt at deep trauma; *i*, 3:40 P.M., immediately after a superficial burn was made over an area 2 by 2 cm. on the apex of the left ventricle anteriorly; *j*, 4 P.M., 20 min. after burn; *k*, 4:40 P.M., 1 hr. after burn; *l*, leads from right border of sternum ($CR_1$) at level of apex and from point 5 cm. to left of sternum at level of apex ($CR_6$) taken at 3:15 P.M.

When segmental elevation occurred, it usually attained its maximal degree in about 30 minutes and then gradually receded over a period of several hours. The diminution in segmental elevation was associated with the development of a deeply inverted T wave. An exception to this usual course of development occurred in 1 experiment, in

which elevation of the RS–T segment in Leads II and III was present in the tracings taken immediately after trauma and persisted undiminished until the animal was killed 6½ hours later.

The paucity of examples of marked segmental elevation in association with deep myocardial lesions contrasts with the frequency with which this type of change was encountered in experiments in which the anterior apical area of the left ventricle was burned superficially with an electrocautery wire (Fig. 2). Significant elevation of the RS–T segment in Leads I, apical IV–R and apical IV–F occurred in each of 6 experiments in which this latter procedure was executed (Fig. 1). Unlike the changes attending deep lesions, the segmental

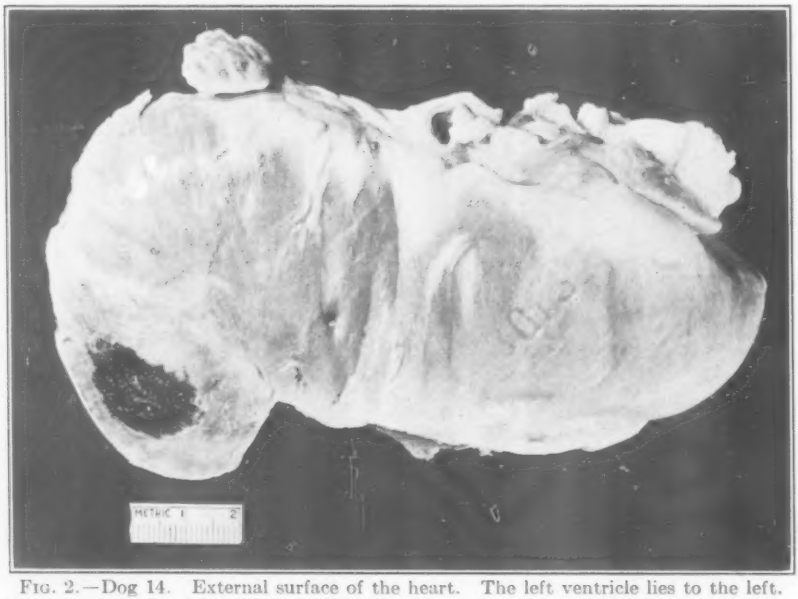

FIG. 2.—Dog 14. External surface of the heart. The left ventricle lies to the left. About 1 cm. to the right and to the left of the apex of the left ventricle are the wounds produced by the traumatizing instrument. The blackened area represents the extent of the burn.

elevation which followed the production of superficial injuries was maximal in the ECG's taken immediately after the injury was produced. Within 1 hour, the level of the segment had returned to the iso-electric line.

Depression of the RS–T segment was also a relatively rare event. Only one really satisfactory example occurred in these 22 experiments. The phenomenon was seen in Leads II and III immediately after trauma and disappeared in 15 minutes.

*Changes in the Configuration of the T Wave.* These changes were inconstant after deep myocardial injuries.

The most significant alterations seemed to be partial, complete or increased inversion of the T wave in the apical IV–R lead. This

change occurred in 13 of 22 experiments. In the remaining 9 experiments the form of this portion of the ECG was unchanged.

Deep inversion of the T waves in Leads II and III occurred in those 2 instances in which the QRS complexes in these leads were increased in height and width.

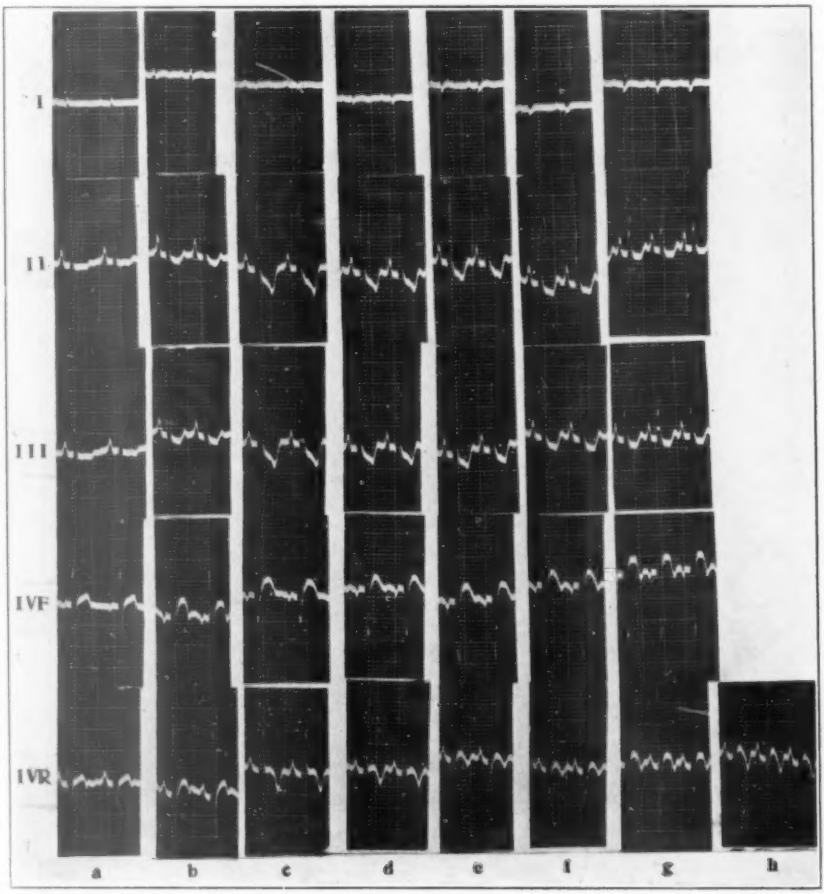


FIG. 3.—Dog. 13. Roman numerals and capital letters represent the leads. *a*, Control after anesthesia; *b*, control after opening chest and pericardium; *c*, 11 A.M., immediately after the first attempt at deep trauma *via* apex anteriorly; the entire lesion was produced at this one attempt; relatively little bleeding ensued; *d*, 12 NOON, 1 hr. after the first attempt at deep trauma; *e*, 12:45 P.M., 1 hr. 45 min. after the first attempt at deep trauma; *f*, 1:40 P.M., 2 hrs. 40 min. after the first attempt at deep trauma; *g*, 4:30 P.M., 5 hrs. 30 min. after the first attempt at deep trauma; *h*, 4:30 P.M., an additional precordial lead in which the exploring electrode was placed 5 cm. to the left of the sternum in the fifth interspace ($CR_6$).

**Comment.** Our results would seem to afford adequate support of the observation that damage to the endocardium and deeper layers of the myocardium of the apical portion of the left ventricle in dogs is

attended by certain changes in the configuration of the QRS complex in a precordial lead designated apical IV–R. Most constant among these changes was reduction in the height of the R wave. The development of a Q wave or of a notch low on the upstroke of the R wave were alternative types of change.

The significance of these observations rests on certain other findings, as follows: (1) An R wave of relatively high voltage was present in all control tracings of the apical IV–R lead. (2) A Q wave was never present in such control ECG's. (3) In control procedures in which a needle was introduced into the left ventricular cavity but no further

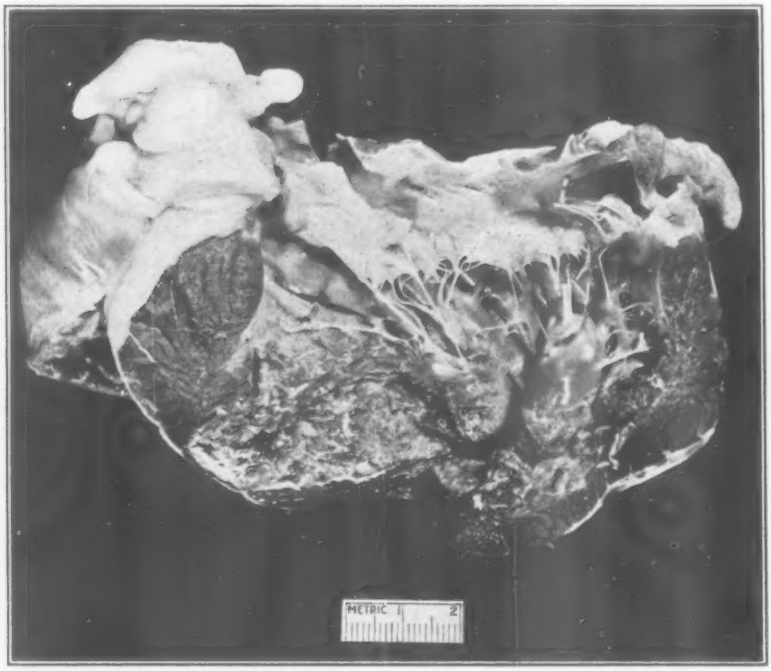


FIG. 4.—Dog 13. Interior of left ventricle. The lesion involves the base of both papillary muscles and the apical portion of the septum.

damage was inflicted, no significant changes occurred in the QRS complex even after several hours had passed (Fig. 5). (4) In those experiments in which the epicardium of the left ventricular apex was burned before production of a deep lesion, the height of the R wave was not altered appreciably.

Reference already has been made to the observation of Wilson and associates[11,13] that in direct leads from regions in which the inner layers of muscle were dead or had been replaced by scar tissue and in which the outer layers were still living and responding to the excitatory process, the QRS group was characterized by specific changes in that portion preceding and including the intrinsic deflection, while the

RS–T segment was not displaced. Limitation of space makes it impracticable to review the theory of Wilson in explanation of the

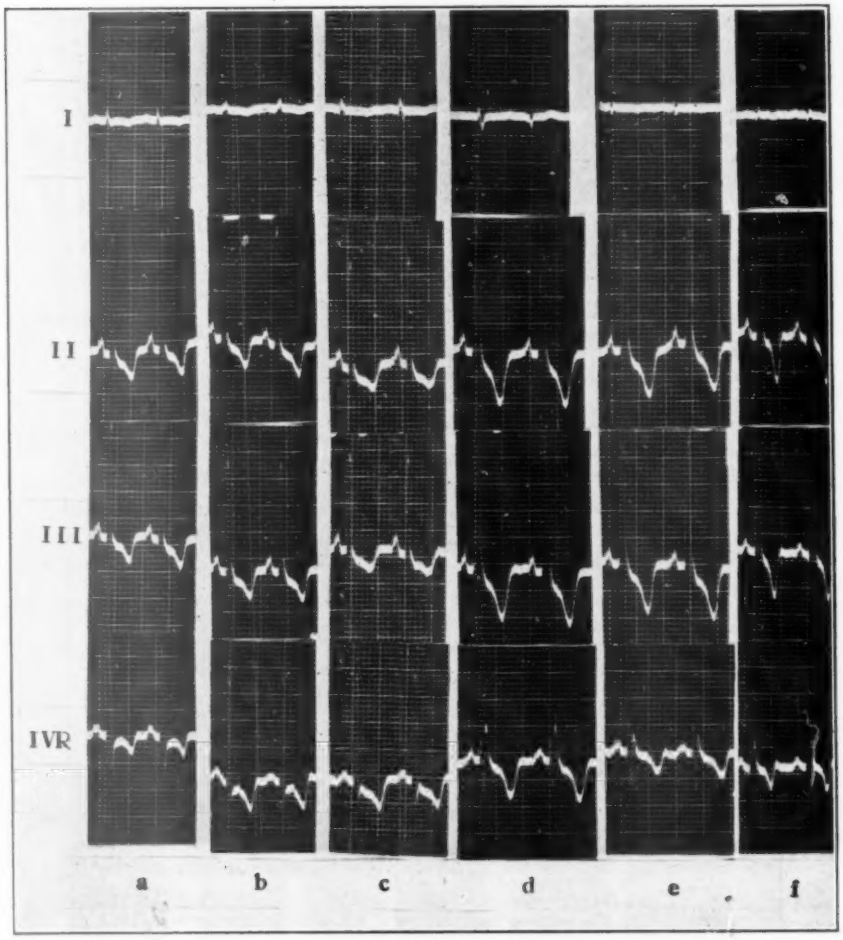


FIG. 5.—Dog 7. Roman numerals and capital letters represent the leads. *a*, 9:30 A.M., control after opening chest and pericardium; *b*, 9:38 A.M., after puncturing the left ventricular cavity *via* the apex anterior with a No. 18 Luer needle, shaking the heart for 1 min., withdrawing 2 cc. of blood and injecting the latter into the anterior surface of the left ventricle just to the left of the interventricular septum; *c*, 12:30 P.M., 2 hrs. 52 min. after control procedures; *d*, 1 P.M., 5 min. after the first attempt at deep trauma *via* apex anteriorly; the lesion was widespread, being deepest in the area just anterior to the anterior papillary muscle and in the apical portion of the septum; the base of the anterior papillary muscle also was damaged and the endocardium was stripped from the base of the posterior papillary muscle; *e*, 1:25 P.M., 30 min. after the first attempt at deep trauma; *f*, 4:25 P.M., 3 hrs. 30 min. after the first attempt at deep trauma.

peculiarities of this curve. The results obtained by him and his associates resemble those here reported in that in both it is the QRS com-

plex in which the characteristic changes occur, and, in both, the intrinsic deflection is reduced in magnitude but not completely obliterated.

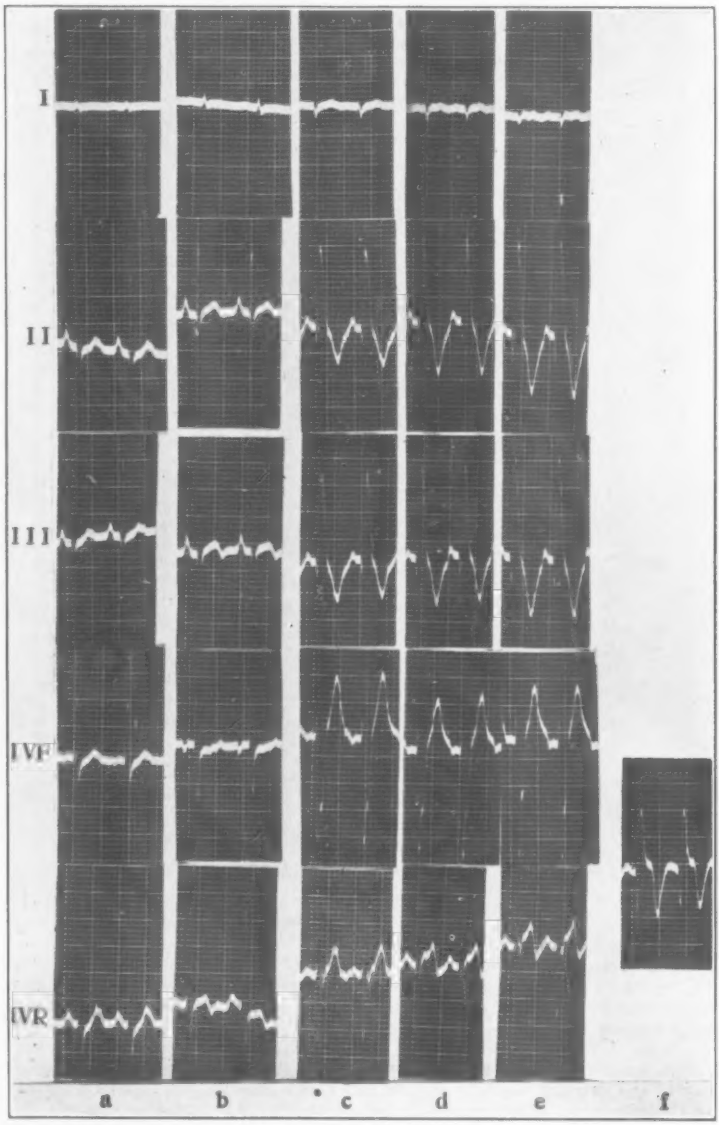


FIG. 6.—Dog 2. Roman numerals and capital letters represent the leads. *a*, Control after anesthesia; *b*, 9:20 A.M., control after opening chest and pericardium; *c*, 9:45 A.M., 10 min. after the first attempt at deep trauma; practically the entire endocardium was removed from the apical two-thirds of the left ventricular cavity (Fig. 7); *d*, 10:30 A.M., 55 min. after the first attempt at deep trauma; *e*, 3:45 P.M., 6 hrs. 10 min. after the first attempt at deep trauma; *f*, 3:45 P.M., exploring electrode 2 cm. to left of left sternal border in the fifth interspace.

The final solution of the source of these changes in the QRS complex must await further developments in the experimental field. They may originate from (1) injury to or destruction of the myocardial fibers underlying the endocardium or (2) damage to Purkinje's network or to the major subdivisions of the left branch of the bundle of His.

A study of the effects of damage of the endocardium and subendocardial myocardium on the width of the QRS complex leads to certain conclusions that appear to be significant. In each of the 22 experiments, there was extensive destruction of those tissues in which portions of Purkinje's system are supposed to lie. In spite of this fact, the width of the QRS complex remained unaltered in 20 experiments. The speed at which the excitatory impulse was propagated remained

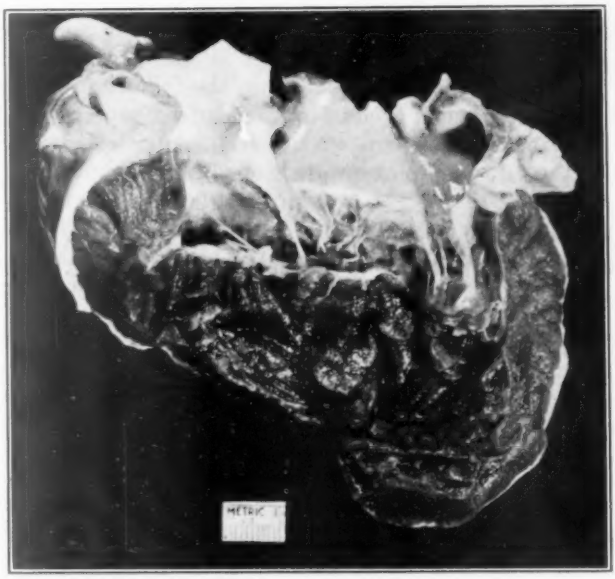

FIG. 7.—Dog 2. Interior of the left ventricle. The lesion extends almost to the free end of both papillary muscles and involves a major portion of the septum.

essentially unchanged, even though the course, as indicated by the form of the QRS complex, was altered. An increase in width of the QRS complex occurred only when the lesion involved an area high on the interventricular septum.

Only a few disconcerting exceptions restrain us from making the generalization that injury to the deeper layers of the myocardium has no appreciable effect on the level of the RS–T segment. We already have indicated our inability to explain these exceptions satisfactorily.

Certainly our results, as shown by the tracings reproduced in Figure 1, indicate that surface lesions exert a dominant influence on the level of the RS–T segment. In the apical IV–R lead, only minimal segmental changes followed the production of extensive deep

myocardial damage, while marked elevation of the RS–T segment occurred when a small superficial burn was made on a portion of the apex overlying the area of deep injury.

Wilson and associates have shown that the ECG effects of damaging deep muscle fibers with a sharp electrode are similar to the consequences of injuring superficial fibers if in each case the electrode is in contact with the damaged cells. If currents of injury are set up when fibers deep in the myocardium are damaged, why are the ECG effects of such currents, that is, elevation of the RS–T segment, so infrequently encountered when semidirect or indirect leads are used? A rather reasonable assumption seems to be that these currents of injury set up in the deep fibers are masked by the normal action currents arising in the uninjured superficial fibers in response to the excitatory process.

As a tentative explanation for the peculiarities of the curves recorded in these experiments in which significant injury was confined largely to the deeper layers of the myocardium, the following hypothesis is proposed: As the wave of excitation spreads from a point high on the septum into the myocardium of the left ventricle, the potentials recorded in the QRS complex are developed. The excitatory process has activated only the deeper layers of the heart when the first part of the QRS complex is inscribed. Hence lesions of the subendocardial myocardium produce changes in this part of the ECG, exhibited without inhibition because of the absence of potential changes in the more superficial layers.

The RS–T segment is inscribed during a period when both endocardial and epicardial regions of the myocardium are involved in the repolarization process. Because of the proximity of the uninjured superficial fibers to the surrounding conductile tissues, the electrical potentials developed here dominate this portion of the ECG, obscuring the effects of any injury potentials developed in the deeper layers of the myocardium. Consequently the RS–T segment has a fairly normal configuration in cases of injury confined to the deeper layers.

Because the process of repolarization may be prolonged in fibers of the injured areas, alterations in the direction of the terminal deflection (T wave) sometimes develop.

Much could be said about the part which unidentified surface injuries may have played in the production of the ECG changes which we have attributed to injury of the deeper layers of the myocardium. This issue was kept in mind throughout these experiments. Two observations are pertinent: (1) The ECG changes which we have ascribed to deep injury differ in kind rather than in degree from those which we and others have related to purely superficial damage. (2) Secondary injuries to surface areas overlying the sites of deep lesions were attended by the development of ECG patterns characterized by the presence of definite segmental elevation, a change which has been ascribed to the effects of trauma on epicardial fibers that are alive and respond to the excitatory process.

**Summary and Conclusions.** Myocardial injuries were produced in dogs by mechanical means. Damage to the endocardium and deeper layers of the myocardium of the apical portion of the left ventricle was attended by certain changes in the configuration of the QRS complex in a precordial lead designated apical IV–R. Most constant among these changes was a reduction in the height of the R wave. The development of a Q wave or a notch low on the upstroke of the R wave were alternative types of change.

These changes in the QRS complex might be derived from: (1) Injury to, or destruction of, the myocardial fibers adjacent to the endocardium; or (2) damage to Purkinje's network or the larger subdivisions of the left branch of the bundle of His.

Although in each of the 22 experiments under analysis there was accomplished an extensive destruction of those tissues in which portions of Purkinje's system are supposed to lie, in 20 experiments the width of the QRS complex remained unchanged. The speed at which the excitatory impulse was propagated apparently remained essentially unchanged, even though its course, as indicated by the form of the QRS complex, was altered. Also, a lesion high on the septum apparently not only is attended by a widening of the QRS complex but also it is the only lesion likely to produce this effect.

Our results indicate that surface lesions exert a dominant influence on the level of the RS–T segment. We have suggested that this circumstance may prevail not because the traumatized subendocardial fibers fail to produce currents of injury, but because the resulting injury potentials are masked by the normal action currents arising in the uninjured superficial fibers in response to the excitatory process.

Changes in the T wave following injuries to the deeper layers of the myocardium were inconstant. The most frequently recurring alteration was an inversion of the T wave in a lead designated apical IV–R.

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# PROGRESS
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# MEDICAL SCIENCE

## MEDICINE

UNDER THE CHARGE OF
JOHN H. MUSSER, M.D.
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## BRONCHIAL ASTHMA: SOME PROBLEMS IN DIFFERENTIAL DIAGNOSIS

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Although the word *asthma* is derived from a Greek expression meaning panting, it has come to represent dyspnea associated with wheezing. It is loosely used to refer to the disease *bronchial asthma*, yet almost all diseases of the lungs, as well as some involving organs lying outside the lungs, may give the symptom asthma, that is wheezing and dyspnea. Rackemann[38a] lists the causes for this symptom as (1) spasm and edema of the bronchial mucous membrane, (2) exudates in the tubes, (3) obstruction by foreign body or tumor, (4) emphysema, and (5) congestive heart failure. Some of the ways in which the word *asthma* has been used are listed by Dorland[12] as follows: cardiac asthma (certain instances of left ventricular failure), Elsner's asthma (angina pectoris), Kopp's, or Wichmann's asthma (thymic dyspnea), steamfitters' asthma (asbestosis) and stone asthma (dyspnea associated with bronchial calculus). Certainly the problem of the differentiation of the diseases producing asthma is primarily that of differentiation of the causes of dyspnea with noisy respirations. Wheezing may be manifested only by sonorous and sibilant râles heard on auscultation so that these findings enter into the differential diagnosis.

The cardinal syndrome producing asthmatic breathing is bronchial asthma, characterized by recurrent attacks of dyspnea which is more marked in expiration and accompanied by wheezing and cough. These episodes result from narrowing of the bronchial lumina from edema of the bronchial mucosa, secretion of a thick exudate into the bronchi, and bronchial muscular spasm from stimuli which, in most individuals, cause no such reactions. The process is usually, in great part at least, a reversible one so that the disease is manifested by episodes of dyspnea. Pathologic findings include the presence of mucinous plugs, an eosinophilic infiltration into the bronchial mucous membrane, hyaline thickening of the basement membrane of the bronchus and hypertrophy of the musculature.[43] Cohen,[8] comparing the reaction to those resulting from experimental histamine injections,[24] described it as exhibiting a characteristic inflammatory reaction. In this light bronchial asthma is a specific and

unusual type of bronchial inflammation generally not infectious in origin and readily reversible. It is a *peculiar* type of bronchitis, which accounts for the difficulty in its differentiation at times from bronchitis of the usual infectious inflammatory type, a reaction not so readily and quickly reversible. Such infection, however, if effecting sufficient narrowing of the lumen, may produce wheezing and dyspnea as does bronchial asthma, as may foreign body in the bronchus, bronchial carcinoma and other diseases for which the treatment is radically different from that of bronchial asthma.

In the diagnosis of bronchial asthma the most important single factor is usually the history. There may be a past or family history of allergic manifestations. Attacks are frequent at night. Certain prodromes may occur, such as plugging of the nose, sneezing, rhinorrhea, burning or heaviness in the chest, gastro-intestinal disturbances, such as heaviness or diarrhea, as well as diuresis, itching and urticaria. The paroxysm gradually reaches its height and, if severe, a sensation of suffocation is experienced. The respiratory rate may go up but frequently respirations are slow and labored. Accessory respiratory muscles are brought into play; the pulse rate is elevated and cyanosis may appear. The jugular and supraclavicular regions, intercostal spaces and epigastrium retract with inspiration. The patient generally complains of difficulty in getting air out, or will do so if asked to analyze his difficulty. Expiration is prolonged, accompanied by an effort, and aided by a contraction of the abdominal muscles. Wheezing is usually associated with expiration and often inspiration as well, and may be loud enough to be heard by bystanders. Cough may occur at or near the termination of the episode. There are small amounts of tenacious sputum containing white masses of mucus. Coëxistent bronchial disease may modify the sputum. Examination of the sputum usually shows many eosinophils and at times Charcot-Leyden crystals, Curschmann's spirals and even bronchial casts. The patient invariably sits up during an attack. Examination of the chest shows bilateral sonorous and sibilant râles, especially on expiration. Expiration is prolonged. There is increased resonance to percussion. Cyanosis may be seen. The attack may last for hours or days and in the recovery period the auscultatory squeaks and groans remain. The episode may be arrested at any stage. If arrested at the beginning, when symptoms are limited to some difficulty in deep breathing, a feeling of oppression, chest constriction and tightness, bronchial asthma may not be diagnosed. The patient may go on with such subjective sensations for a considerable period of time before episodes advance to a stage in which sonorous and sibilant râles suggest the diagnosis. The sense of constriction and the mild dyspnea may lead the patient to suspect heart disease or bronchial disease other than asthma. If arrested after the appearance of sonorous and sibilant râles, but before the attack progresses to its peak, the episode may be confused with other conditions itemized below, particularly the bronchial syndromes.

The patient usually presents himself with the above story of paroxysmal attacks of dyspnea, usually with wheezing and cough. Such episodes may have been frequent or rare, and long or short in duration. Hay fever or other known allergic manifestations may have been present. The diagnosis then may be simple and easy, and usually is. Yet errors in diagnosis are extremely important for, as already stated, the therapy of conditions simulating bronchial asthma is usually entirely different and at times the condition is a correctable one which, when treated, disappears. If the patient has had only one attack, the diagnosis is likely to be in

more doubt and further observation may be necessary. The patient may present himself for examination between attacks, and, when there is doubt about the diagnosis, a complete examination is necessary, including investigation of the blood and urine, chest roentgenogram, a complete cardiac work-up and, at times, even laryngoscopy and bronchoscopy.

Commonly grouped with those diagnosed as asthmatics are other patients not giving the classic picture sketched above. These patients usually do not have an onset early in life, a family or past history of allergic manifestations, positive skin tests or environmental control.[8] Onset of asthmatic breathing is usually in middle age, often preceded by months or years of spasmodic cough. Infections of the nose, throat, or bronchial tree may have accompanied the episodes of cough and bronchitis. Age usually helps to differentiate these patients but not always. Such asthmatic episodes may occur in children without family or past histories of allergy and may follow whooping cough, measles, or other respiratory infection. Such children have a gradual onset of attacks and may not be well in the intervals.[33] The term *infective asthma*, or *asthmatic bronchitis*, is often applied to this picture. However, these episodes are much commoner beyond the age of 40 and in some of the patients causative factors leading to the asthmatic episodes are not at all well established[38c] even though chest infection, paranasal disease and many other factors are sought. Past and family histories of allergy are only occasionally elicited; allergens as a cause are rarely found, and response to anti-allergic treatment may be poor.[1] As Alexander pointed out, the symptoms may start with a cough and mucoid sputum, which may last for weeks, with a few musical râles. Recovery may occur with later repetition, often with frank wheezing. With repeated episodes response to iodides and epinephrine may become less dramatic. Cough, at times with wheezing, may persist between the episodes, which become less clear-cut in onset or disappearance. More inspiratory distress is often evident. The lack of seasonal variations, environmental control, histories of allergy and positive skin tests has lead to the belief that these patients have within themselves the cause of their asthmatic episodes. The term *intrinsic asthma* is applied in contradistinction to extrinsic, or typical bronchial asthma in which the causative factor arises in the environment. Rackemann[38b] has been particularly interested in this group. He has found no satisfactory theory to explain these cases but does divide them into 3 groups: (1) a picture closely related to acute respiratory infection, the disappearance of which is followed by a receding of the asthmatic symptoms, which recur with a repetition of the infection, and which is termed *asthmatic bronchitis;* (2) a group with no relationship to season, environment, or diet, with no known allergic relationships; and (3) patients with evidence of emphysema, bronchiectasis or heart disease with asthma as a result of bronchial exudate, spasm, or edema, occurring as a part of the primary disease.

As already stated, the history and clinical picture of bronchial asthma may be so characteristic that the diagnosis is easily made, often by the patient before he sees the physician. But occasions arise when there is confusion with other diseases or when other diseases may be mistaken for bronchial asthma. The presence of other disease may overshadow the asthmatic picture[23] or *vice versa*. The great and important differences in treatment and prognosis of many of these conditions demand that they be ruled out. Maytum[30a] has listed these conditions according to systems and his table is reproduced here (Table 1). With this array of con-

ditions producing dyspnea and simulating asthma, it is obvious that the great differences in treatment demand adequate differentiation.

TABLE 1.—MAYTUM'S LIST OF CONDITIONS THAT MAY SIMULATE ASTHMA

**A. Respiratory System.**

I. LARYNX.
1. Laryngeal spasm:
   *a.* Spasmodic croup
   *b.* Laryngismus stridulus
   *c.* Laryngeal crisis of tabes dorsalis
2. Inflammation:
   *a.* Acute (acute laryngitis, diphtheritic laryngitis)
   *b.* Chronic (tuberculosis, syphilis)
3. Angioneurotic edema
4. Paralysis of the vocal cord
5. Laryngeal stenosis
6. Foreign body
7. Neoplasm:
   *a.* Benign
   *b.* Malignant

II. TRACHEA AND BRONCHI.
1. Intrinsic lesions:
   *a.* Acute and chronic bronchitis
   *b.* Chronic inflammation with stenosis (bronchiectasis, tuberculosis, syphilis, foreign body)
   *c.* Neoplasm (benign; malignant)
2. Extrinsic lesions:
   *a.* Substernal enlargement or carcinoma of the thyroid gland
   *b.* Enlargement of the thymus gland
   *c.* Aneurysm of thoracic aorta
   *d.* Tuberculous tracheobronchial nodes
   *e.* Mediastinal neoplasm (benign; malignant)

III. LUNG.
1. Inflammation:
   *a.* Pneumonia
   *b.* Tuberculosis
   *c.* Pneumoconiosis and pulmonary fibrosis
2. Idiopathic pulmonary emphysema
3. Neoplasm of lung and pleura
4. External pressure:
   *a.* Pneumothorax
   *b.* Hydrothorax

**B. Circulatory System.**

I. CARDIAC DECOMPENSATION

II. CORONARY SCLEROSIS

III. PAROXYSMAL AURICULAR FLUTTER OR FIBRILLATION; PAROXYSMAL TACHYCARDIA

**C. Renal System** (manifested in circulatory system).

**D. Nervous System.**

I. FUNCTIONAL AIR HUNGER

II. HYSTERICAL POLYPNEA

III. RESPIRATORY SYNDROME FOLLOWING ENCEPHALITIS

Difficulty in breathing associated with some type of noisy respiration accounts for the confusion of most of these conditions with bronchial asthma. This is true with *laryngeal disease*. The dyspnea of laryngeal obstruction is characterized by retraction on inspiration of the area of the suprasternal notch and at times the ribs, supraclavicular and epigastric regions as well. This, with inspiratory stridor is a distinctly inspiratory disturbance. If any doubt arises, direct laryngoscopy will settle the

diagnosis. Such findings as these may occur in the child with congenital deformities of the larynx, laryngeal or tracheal stenosis, or both, as seen after high tracheotomy, trauma, diphtheria, or surgical infections, and in laryngeal spasm. Spasm is occasionally a part of the picture of spasmophilia, evidences for which (Chvostek's sign, electrical excitability, changed blood calcium levels) may be sought. Spasmophilia in children with asthma-like episodes was described by Lederer[26] as *bronchotetany*. Neoplasm, foreign body, paralysis of the vocal cords and edema of the larynx give similar pictures, with hoarseness, croupiness, at times with special characteristics peculiar to each such as history of foreign body or evidences of angioneurotic edema. Acute inflammations are likely to be accompanied by tracheitis and other evidences of inflammation, including systemic findings. Inspection of the laryngeal cavity should be done when doubt exists. Retropharyngeal abscess may produce similar symptoms and should be diagnosed by the local examination.

*Bronchial disease* of many types simulates bronchial asthma. Foreign body in the bronchus may produce wheezing respiration which is mistaken for bronchial asthma, especially if a history of foreign body is not evident. Jackson[21] stressed the *asthmatoid wheeze*, a dry wheezing sound heard with the ear close to the open mouth during expiration. Foreign body in the stem bronchus is likely to show unilateral physical findings, a most important differential point, and roentgenologic evidences may be present even if the foreign body is not radiopaque. Intracheal foreign body may produce a snapping sound heard at the mouth when the patient coughs and a thud may be felt in the subglottic area over the trachea. Tracheobronchial stenosis of any type may be mistaken for asthma. Stridor, localization of findings, and bronchoscopy will make the diagnosis.

Acute infectious laryngotracheobronchitis in children produces stridor and an ashen gray color with a croupy cough, signs of laryngeal and bronchial obstruction and a febrile response. Gummy ropy secretions are present and require bronchoscopy for removal. Neoplasm of the bronchus also may produce noisy respiration and dyspnea.[25] Here again the history, physical and roentgenologic findings should suggest the diagnosis and bronchoscopy should, if necessary, be employed to establish a diagnosis. Benign tumors, as well as bronchogenic carcinoma, may be mistaken for bronchial asthma. Shortness of the duration, and localization of findings to one side should lead to roentgenologic and bronchographic studies, if necessary. Benign tumors are likely to give a longer history than the malignant type, and thus may simulate bronchial asthma more closely.

Bronchogenic tumors are among the many conditions which simulate bronchial asthma and which are diagnosed only by careful study. Bronchoscopy is particularly indicated when such tumors appear as possible causes for the picture. Clerf[7] and Friedberg[15] have pointed out these problems very clearly. They have shown that the bronchi elongate and expand in inspiration and contract and shorten in expiration. For this reason pathologic processes which narrow, or partially block, the bronchial lumina will interfere especially with the outflow of air. Friedberg reaffirms the statement that endoscopy is warranted in any case of "atypical bronchial asthma" which does not respond readily to diagnosis and therapy.

Prickman and Moersch[37] have pointed out certain instances when bronchoscopy is extremely helpful in the diagnosis of bronchial asthma, such as in the occasional case of bronchostenosis which they feel is a more

common complication of both allergic and so-called infectious asthma than is generally believed. They have found definite localized stricture-like narrowing of a bronchus, or bronchi, in certain instances with impaired flow of air beyond the stricture and retention of secretions and even partial or complete atelectasis. These findings were present in 60 of 140 patients with asthmatic episodes who were specially selected for bronchoscopy. Certain clinical findings, characteristic symptoms, and physical and roentgenologic observations may lead to the suspicion of bronchostenosis. Severe persistent and sometimes paroxysmal cough which aggravates the asthma is such a symptom. There is difficulty in raising the sputum even with severe cough only to have a profuse sputum later. The sputum is mucopurulent and, in 40% of Prickman and Moersch's patients, at some time blood streaked. Febrile episodes, either with or without chills occurred in 68% of their cases. It was usually moderate and lasted several to many days, to be followed by an increase in sputum on its subsidence. Leukocytosis was usual.

The above history, or parts of it, should arouse suspicion of bronchostenosis or some other complication. Likewise, 53% of Prickman and Moersch's series gave a history of pneumonia, and 35% a history of pleurisy. Bronchostenosis was frequently mistaken for bronchopneumonia because of fever, cough and purulent blood-tinged sputum, and evidence of atelectasis. Repeated episodes of pneumonia with asthma should lead to suspicion of bronchostenosis and to bronchoscopy. It is only a small percentage of patients with asthma that need bronchoscopy and bronchostenosis should be added to the list of diseases which, when suspected, are to be ruled in or out by this means.

In children with acute tracheal and bronchial inflammation, wheezing may develop and the chest sounds "asthmatic." Simple infection without allergic background may cause sufficient narrowing to produce these signs and the differentiation may be difficult unless the patient is studied for a period of time. This process starts slowly and ends gradually. There are no paroxysms and signs of infection are present. In older individuals with chronic bronchial disease, bronchitis, bronchiectasis, and emphysema, particularly with superimposed infection, dyspnea with wheezing may develop. To determine whether mechanical narrowing alone is the causative factor or whether bacterial hypersensitiveness also acts as an exciting factor becomes the problem, which has already been discussed. In patients with known bronchial asthma for long periods of time, especially those in whom chronic bronchitis has developed or in those with intrinsic asthma, attacks may become refractory to treatment, the so-called *status asthmaticus*. Fever and signs of infection may appear, often with purulent bronchitis and thick ropy secretions in the smaller bronchi or with peribronchial pneumonia. The recognition of such complications is important to proper therapy. Alexander[1] has pointed out the frequency of status asthmaticus and of marked eosinophilia in intrinsic asthma. At autopsy at times eosinophilic infiltrations have been found in the bone marrow and myocardium.[6]

The association of eosinophilia and periarteritis nodosa with asthmatic episodes is most interesting. Alexander[1] has called attention to its frequent presence in status asthmaticus. Harkavy[17] has also pointed out its occurrence and Rackemann and Mallory[39] found in a series of 50 cases of fatal asthma 5 with periarteritis nodosa, a high figure for the incidence of this disease. Lichtman and his associates[28] noted the fact that asthma is said to occur early in about 15 to 20% of the cases of periarteritis nodosa

and eosinophilia may reach 70 to 80%, a finding which may be a clue to its diagnosis.

Some evidence to indicate a possible relationship of periarteritis nodosa to allergic phenomena rests in a report of Rich[40] in which he records the observation of periarteritis nodosa in patients dying of acute infection when serum sickness was also present. He indicated that vascular lesions of this type can be a manifestation of the anaphylactic type of hypersensitivity. In a report with Gregory[41] he presented experimental evidence of the disease in rabbits which had been treated with foreign protein. Later Selye and Pentz[44] by chronic severe overdosage with desoxycorticosterone acetate produced in animals lesions similar to those of periarteritis nodosa. It would appear that periarteritis nodosa is not a disease entity itself, and although its etiology is not definitely established, a relationship to allergic phenomena is very possible.

Involvement of the *lungs* with disease which produces dyspnea, especially if noisy respirations of one type or another occur, is often confused with bronchial asthma. Lamson, Butt and Stickler's[25] autopsy series of a group of patients with asthma includes many of these conditions, such as carcinoma, pneumoconiosis and tuberculosis. Pulmonary emphysema is most difficult to differentiate at times. History may be most important, for typical bronchial asthma often produces emphysema. The dyspnea of emphysema may occur in paroxysms during infection but most often develops slowly over long periods of time; effort is definitely a precipitating factor producing wheezing respirations. Foreign bodies in the bronchi causing pneumonitis have already been mentioned. In pneumoconiosis paroxysms of dyspnea are not clear-cut and historical data leading up to the development of the picture are most helpful. Roentgenograms of the chest are important. Roentgen ray and radium therapy to the chest may produce asthma-like dyspnea. Hydatid cysts may produce asthmatic breathing and eosinophilia and urticaria may be present. Asthmatic dyspnea has been described as the sole presenting symptom of generalized endolymphatic carcinomatosis,[31] in which metastases are found to the pulmonary lymphatics and in which the Roentgen picture is a pattern of thin lines often with reticulation extending from the hilum toward the periphery. Actual nodules may not be present and the picture may simulate that of pneumoconiosis, miliary tuberculosis, lymphoma or fibrosis resulting from infections.

It is to be remembered that bronchial asthma may be the underlying cause of certain pulmonary changes.[9,32,36] Edema and spasm of the bronchi, together with mucinous plugs, are known to produce areas of atelectasis and even massive collapse of the lung[36] with relief by bronchoscopy. In 1935, H. Miller and his associates[32] described a group of 11 allergic children with *allergic bronchopneumonia*, changes in the lung which they felt resulted from bronchial obstruction, allergic reactions of the lung parenchyma, or both. Frequently changing physical and Roentgen signs characterized the pictures. Fever occurred. Common diagnoses on these patients had been asthmatic bronchitis, recurrent bronchitis, bronchopneumonia, abortive bronchopneumonia, non-tuberculous pulmonary infection, tuberculosis, perifocal tuberculosis, bronchiectasis, pulmonary abscess and foreign body.

In 1932, Löffler described a syndrome of transient pulmonary infiltration with associated leukocytosis and eosinophilia found especially in allergic individuals. In 1936 he reported 51 cases.[29] Since then there have been numerous reports on this picture.[14,16,20,22,42,45,51]. Hansen-Pruss

and Goodman[16] have summarized the features of this picture as: (1) occurrence in allergic people, (2) varying degrees of leukocytosis and eosinophilia, (3) afebrile course, (4) pulmonary consolidation, (5) persistent severe asthma, (6) lack of response to sulfa drugs, and (7) history of frequent respiratory disease. The generally benign nature of Löffler's cases contrasts with some of those described by Miller and his group.[32] The roentgenograms of the chest are especially important. Varying shadows of different sizes, shapes and location, either unilateral or bilateral, may on single films be indistinguishable from those seen in tuberculosis. Serial films may be necessary for differentiation. Eosinophilia does not parallel the chest infiltrations. Löffler felt that bronchial asthma with partial atelectasis, tuberculosis, pneumonia, and infarction were not part of the picture. He considered ascariasis a possible cause, and others since then have found worm infestations and amebiasis associated with the picture. A possible relationship of so-called tropical eosinophilia to these pictures must be considered.[46]

The relationship of tuberculosis to asthma has received much attention. Tuberculosis of the lungs may produce respiratory distress in many ways, through the pressure of tracheobronchial nodes, by fibrotic contraction or adhesions producing mediastinal shifts, mechanical embarrassment of the cardiovascular system, tracheal and bronchial compression or tugging and by bronchial strictures.[52] Tuberculous tracheobronchial nodes are most likely to cause compression in children especially before the 2nd year. Dyspnea may be exertional but is constant and does not respond to epinephrine. Tuberculin tests and roentgenographic studies will help in differentiation. Tuberculosis may also coëxist with bronchial asthma and the latter may mask the former. There has been much controversy as to possible causal relationships when the two occur together (*tuberculo-allergic asthma*).[50] General views are that causal relationships between the two are either infrequent[13,50] or entirely absent. In 1 series[50] of 452 asthmatics pulmonary tuberculosis was present in 25 (5.5%). On the other hand some feel that tuberculosis is no more frequent in asthmatics than in the general population[23] and that tuberculosis plays no particular etiologic rôle in the production of the asthma, at least no more than other respiratory infections which render the mucosa vulnerable. In 1 series[49] the incidence of asthma among 386 patients with active tuberculosis was 3.1%, a figure which approximates the reported incidence of asthma among the rest of the population. Sprague[47] believes that bronchial asthma and pulmonary tuberculosis appear as coëxisting diseases much more frequently than either the literature or the experience of the general practitioner would show. There is a tendency to regard the asthmatic as "just another asthmatic." Each individual case, if studied, may reveal changes which cause the physician to suspect tuberculosis. Anorexia, unusual loss of weight, fever, change in character of cough, amount and type of expectoration, bloody sputum, sweats, tuberculosis contacts, elevated pulse rate, secondary anemia, physical findings other than those of typical asthma, should lead to Roentgen ray studies. The entire problem of tuberculosis and asthma has been reviewed by Tocker and Davidson.[49] One must be alert to this complication.

*Intrathoracic disease* of other types may simulate bronchial asthma. Tumors of the mediastinum, substernal goiter, inflammatory disease, mediastinal abscess, Boeck's sarcoid,[3] enlargement of the peribronchial or mediastinal lymph nodes, as in Hodgkin's disease, and aneurysm of the aorta must be considered. The dyspnea ascribed to thymic enlarge-

ment accompanies other manifestations of that picture. In aneurysm and mediastinal tumors, for example, attacks may be paroxysmal. Other evidences of disease than asthmatic breathing, for example stridor, hemoptysis, signs of mediastinal pressure, should be sought, but differentiation may require roentgenograms and even bronchoscopy, as well as history and physical examination.

*Cardiac asthma* is one of the manifestations of left ventricular failure and is often called paroxysmal nocturnal dyspnea. It simulates bronchial asthma in some respects, at times very closely, and is one of the most important differentiations in older patients. Although cardiac asthma, like bronchial asthma may come on during the day, it is most common, again like bronchial asthma, at night. The dyspnea may simulate very closely that of bronchial asthma, but respirations are often more rapid and on occasion the frothy pink sputum of pulmonary edema is present. Chest findings may be those of typical bronchial asthma and differentiation is then difficult. Moist basal râles may be present, alone or with sonorous and sibilant râles. Occasionally nothing abnormal is heard on auscultation. Other evidences of heart disease, enlargement of the heart, significant murmurs, precordial pain, evidences of heart failure in the past or at present, edema, may occur but at times it may be impossible to distinguish bronchial from cardiac asthma on history and physical grounds unless the patient is followed for some time. Sputum studies for eosinophils and determinations of the circulation time are helpful.

The circulation time, especially from arm to tongue, has been studied extensively in cardiac failure and to some extent in bronchial asthma. The findings of Hitzig, King and Fishberg[19] in 1935 of an arm-to-tongue time ranging from 18 to 60 or more seconds in cardiac failure have been amply confirmed. Occasionally exceptions are found and such patients occasionally have a normal circulation time. In bronchial asthma the time has been reported as not prolonged or even as accelerated.[4] Cottrell and Cuddie,[11] using decholin, found the arm-to-tongue time in bronchial asthma to vary from 10 to 15 seconds. The figures were normal both during attacks and in the intervals between asthmatic episodes.

Cardiac asthma is most common in the older patient, especially beyond the age of 50, a time when bronchial asthma is less likely to have its onset, only about 15% starting in the 5th and 6th decades. Eosinophilia in the blood and sputum favors bronchial asthma, but occurs in other diseases and when heart disease is a complication of bronchial asthma. Physical examination of the lungs may show basal râles or pleural effusion which usually mean heart disease. Levine[27] stresses the presence of basal moist râles and the absence of diffuse sonorous and sibilant râles as a differential point. When present these findings are extremely helpful. The finding of evidences of heart disease producing strain upon the left ventricle, either by physical or roentgenologic examination, establishes the etiologic agent for cardiac asthma and favors heart disease as a cause of the picture. Elevated venous pressure, if present, falls in the same group. The absence of allergic manifestations, some already mentioned above, is also helpful. An attack of cardiac asthma may terminate after epinephrine has been given but not as uniformly as does bronchial asthma.

It must be remembered that heart disease may occur in the patient with bronchial asthma, either by coincidence or as the result of the bronchial asthma. That bronchial asthma may be important in the production of heart disease is debated. The general consensus is that heart disease from such cause is not common,[2,10,25,35,48] although the cor pulmonale

type of cardiac damage with right ventricular hypertrophy and even failure has been reported on this basis.[10,43] Harkavy and Romanoff[18] have reported electrocardiographic changes which are in large part not extensive and are reversible. Schiller, Colmes and Davis[43] found that cardiac changes resulting from chronic bronchial asthma are more common than is generally believed. Of 12 autopsied cases with bronchial asthma of 6 or more years' duration, 5 died in congestive heart failure and 4 of these showed predominant hypertrophy of the right ventricle. They pointed out that the diagnosis of circulatory failure in such patients is difficult because of dyspnea caused by emphysema. Some show no edema, and when it does occur, it may appear suddenly and progress rapidly.

Paroxysmal cardiac irregularities, especially auricular fibrillation and flutter and paroxysmal tachycardia, may produce episodes of dyspnea, but other characteristics, especially on examination of the patient, will easily differentiate them from bronchial asthma.

Disturbances outside the respiratory tract and the thoracic cage may be confused with bronchial asthma. This is true of sighing respiration and *hysterical respiratory distress*, both of which bear some superficial resemblances to bronchial asthma. Hysterical overbreathing, which may give symptoms of hyperventilation, is easily differentiated when the patient is seen in an attack. There may be a close association with emotional factors or fatigue. (This may occur at times with bronchial asthma.) Polypnea with rapid respirations, rather than the slow labored dyspnea of bronchial asthma, is present. There is no sputum; typical auscultatory findings are not present; attacks may be of short duration; and onset and offset of attacks are more abrupt than in bronchial asthma. When the patient is seen between episodes, some observers[34] have injected vagotonic drugs (mecholyl) which are likely to precipitate attacks of bronchial asthma, for differentiation. Other evidences of hysteria should be sought as well.

The syndrome of *sighing respirations*[5,30b] may accompany hysteria or other psychoneuroses, but not necessarily so. Stable individuals under unusual circumstances may also present this picture. Episodes of difficulty in breathing occur and bronchial asthma may, therefore, be suspected. Occasional sighing respirations are common, especially in nervous and neurotic individuals. The patient feels that he or she cannot get air into the chest. In emotional upsets or during periods of mental stress and strain, such respirations are likely to be more frequent. Repeated persistent rapid "attacks" may occur. A feeling of pressure is often present and the patient places his hands over the chest to show its presence. Shallow respirations are followed by deep sighing respirations easily recognized when seen. If frequent and repeated, such sighing attracts the patient's attention. He feels distress, feels suffocation, and may want to get out into the air or open a window. He may become pale and perspire. While occurring often during the day, such attacks may appear at night and especially then is bronchial asthma suspected. Overbreathing may lower the alveolar carbon dioxide and thereby cause alkalosis. When the patient is seen in an attack the respiratory distress is easily recognized. Respirations are deep and sighing, similar to those occurring occasionally between attacks. The rate may not be rapid but accessory respiratory muscles may be used. There is no cough, wheezing or sputum. Symptoms of tetany may develop, such as lightheadedness, vertigo, paresthesias, tingling of the fingers and toes, precordial distress,

sense of constriction of the thorax and sometimes carpopedal spasm and spontaneous facial twitchings. These may be reproduced if the patient deliberately overbreathes for 15 to 20 respirations.

*Postencephalitic hyperpnea*[33a] may simulate bronchial asthma for it is accompanied by forced breathing. The breathholding and other associated postencephalitic findings will permit differentiation.

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# NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF
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## THE AMYTAL INTERVIEW

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The effectiveness of narcosis in revealing buried memories and conflicts has been recognized for hundreds of years, in fact as long ago as man has written about the effects of alcohol upon man. Much of the so-called newness of our narcosis treatments is a newness of terminology and a revival of older enthusiasms. Anesthetists long have remarked about how patients will reveal personal material and unrecognized facets of the personality during the induction phases of an anesthetic. The beneficial effects of emotional catharsis under the influence of an alcohol narcosis have been observed long before the treatment value of emotional episodes under newer narcotic methods was formalized into a new array of terms and esoteric discussions.

The newer methods of narcosis have been variously termed "narcoanalysis," "narcosynthesis," "narcohypnoanalysis," "amytal interviews," and so forth. Horsley invented the term "narcoanalysis" in 1936,[1,2] and the term "narcosynthesis" was described by Grinker and Spiegel.[3] Bechterew had suggested that hypnosis, narcosis and sleep were closely allied.[4] As he pointed out, it is not readily easy to distinguish the differences between narcosis and hypnotic sleep. In fact, it is our opinion that the better results are obtained when the reactions of the narcotized patient are identical with similar reactions under hypnosis without the use of drugs. We do not agree with Grinker and Spiegel in differentiating the narcotic effects as distinct from hypnosis.[3]

Effective reliving and recovery of past experiences with amytal is similar to the use of hypnotic techniques without the benefit of drugs. In fact, barbiturates facilitate hypnosis for many subjects. Hypermnesias, catalepsy, anesthesias, and post-treatment amnesias may be demonstrated while the patients are under the influence of amytal narcosis. In other words, the amytal interview is largely another hypnotic therapy.

Practically all of the modern barbiturates have been tried in various clinics. Chloroform, Cannabis Indica, paraldehyde, scopolamine and chloral often have been used for similar purposes.[5,6,7,8] We prefer to utilize the specific term, the amytal interview, because of greater acquaintance with the actions of the drug. Intravenous sodium amytal is preferred to pentothal because it is thought that one may prolong the milder levels of diminished awareness, when the usual techniques of hypnosis and suggestion may be reiterated over longer periods. There is no difficulty with "hang-over" effects from sodium amytal, if sufficient caffeine

sodium benzoate is used at the end of the treatment. Furthermore, it has been noted that one may suggest a selective recall of actions and discussions under amytal narcosis, like with hypnosis, more readily than with pentothal narcosis, largely because the lighter levels of narcosis are better controlled.

Hypnosis was used effectively in World War I, but for many reasons, technical, social and personal, few medical officers had acquired sufficient acquaintance with hypnotic techniques to use them effectively in World War II. The phenomena described by Grinker, Spiegel and others under the fancier terms of today were described by workers of the last war as manifestations of hypnotic therapy.

Brown,[9] Hadfield,[10] Taylor,[11] and Ross[12] were some of the enthusiastic exponents of the abreaction under hypnosis, which has acquired many semantic variations throughout the last 2 decades to become something "new."

The physiologic actions of the barbiturates on the cerebral cortex are well outlined by Brazier and Finesinger:[13]

"The work of Quastel and associates (Quastel, J. H., and Wheatley, A. H. N.: Narcosis and Oxidation of Brain, *Proc. Roy. Soc.*, London, **112**, 60, 1932; Davis, D. R., and Quastel, J. H.: Dehydrogenations by Brain Tissue: Effects of Narcotics, *Biochem. J.*, **26**, 1672, 1932; Quastel, J. H.: Respiration in the Central Nervous System, *Physiol. Rev.*, **19**, 135, 1939) has shown that narcotics even in low concentrations inhibit specifically the oxidation *in vitro* by brain cells of d-glucose, lactic acid and pyruvic acid. This inhibitory action takes place, not by preventing the access of oxygen to brain cells nor by interfering with the activation of oxygen by brain catalysts, but by impairing the hydrogen-liberating mechanisms (dehydrogenase activity) which normally result in activation of lactic or pyruvic acid.

"Narcotics inhibit this dehydrogenase activity, presumably by forming surface films or adsorption compounds which prevent the access of hydrogen donators to their activating enzymes. (Sen, K. C.: The Effect of Narcotics on Some Dehydrogenases, *Biochem. J.*, **25**, 849, 1931.) Thus, the effect of the narcotic is to diminish the ability of the brain cells to oxidize lactic or pyruvic acid or d-glucose. The access of oxygen to the cell is quite unimpaired, but the diminished oxidizing ability of the cells results in a lowering of the amount of energy available for these cells to accomplish their functional activities. This depression of the normal functional activity of the cells in question results in, or is, 'narcosis.'

"The chain of oxidative processes in brain cells may be represented in outline by the following simplification: At the beginning of the chain the principal substrate is d-glucose, which, through a long chain of intermediary changes, is finally oxidized to carbon dioxide and water, with liberation of large amounts of energy. One of the chief intermediary stages in the first part of the breakdown of d-glucose is the oxidation of lactic acid to pyruvic acid. Meyerhof (Ueber die Atmung der Froschmuskulatur, Arch. f. d. ges. Physiol., **175**, 20, 1919) showed the dependence of this stage on the presence of a coenzyme which acts as a specific carrier linking lactic dehydrogenase with lactic acid in such a way that the dehydrogenase can remove hydrogen from the lactic acid, with the production of pyruvic acid. The dehydrogenase which activates lactic acid as a hydrogen donator is highly specific. (The dehydrogenase which activates lactic acid has been isolated, and its chemical constitution is known.—Schlenk, F.: Whither Enzyme Chemistry, *Texas Rep. Biol. and Med.*, **2**, 183, 1944) and is present in greater quantities in brain than in muscle (Green, D. E., and Brotteaux, D.: Lactic Dehydrogenase of Animal Tissues, Biochem. J., **30**, 1489, 1936).

"It is this stage of dehydrogenase activity which is inhibited by narcotics of the barbiturate type. To repeat, these narcotics do not interfere with the catalytic activation of oxygen, or with the access of oxygen to the brain cells, but inhibit the activity of the dehydrogenase stages of pyruvic and lactic acid metabolism.

"The mechanism of this dehydrogenase activity may well be, as Quastel and

Wooldridge (Some Properties of Dehydrogenating Enzymes of Bacteria, *Biochem. J.*, **22**, 689, 1928) suggested, a polarization of the molecule of the substrate by an electric field at the cell surface to which the molecule is attached. If the polarization is sufficient, the molecule will receive its critical energy of activation and will then be able to function as a hydrogen donator.

"This chain of events in the cell respiration of brain tissue has been worked out from data gained from *in vitro* experiments with minced fresh brain and with brain slices, variations of the Barcroft and Warburg technics (Dixon, M.: Manometric Methods, London, Cambridge University Press, 1934) being used for the most part. To extend these studies to the respiration of brain cells *in vivo* necessitates some other technic. Electroencephalography may well furnish pertinent data in this field.

"The work of Hoagland (*a.* Hoagland, H.: Chemical Pacemakers and Physiological Rhythms, *in* Alexander, J.: Colloid Chemistry, New York, Reinhold Publ. Corp., vol. **5**, 1944; *b.* Pacemakers of Human Brain Waves in Normals and in General Paretics, *Am. J. Physiol.*, **116**, 604, 1936; *c.* Hadidian, Z., and Hoagland, H.: Chemical Pacemakers: I. Catalytic Brain Iron; II. Activation Energies of Chemical Pacemakers, *J. Gen. Physiol.*, **23**, 81, 1939) demonstrated clearly the influence of changes in brain cell respiration on the frequency rates of cortical potentials. It is probably that cortical cells build up potential gradients in the process of their respiratory metabolism, and, as Hadidian and Hoagland (*c.* above) stated:

"These may be of the nature of diffusion potentials across cell membranes which possess definite electrical impedence and which discharge when the potentials reach a critical value. In such a system the discharge frequency depends on the speed with which the metabolic factor can load the capacities of the cell walls to their critical discharge potentials. The absolute frequency would thus depend on the rate of cellular respiration and on the electrical impedence of the cell walls. . . . ."

The technique of the sodium amytal interview is simple. Dilute 15 gr. (1 gm.) of sodium amytal in 30 or 40 cc. of distilled water. Place this solution in a large enough syringe and use a small gauge intravenous needle to provide further protection against too rapid administration of the drug. The solution should not stand for over 30 minutes before use, and it should be clear. In fact, it is preferable to check the preparation of the solution to be sure of proper mixing and proper dosage.

Always have $7\frac{1}{2}$ gr. of caffeine sodium benzoate ready in a hypodermic syringe in case of untoward reactions or too deep a narcosis. At the completion of the interview it is well to administer $7\frac{1}{2}$ gr. of caffeine sodium benzoate subcutaneously to assure one against prolonged deep narcosis and to facilitate the return of awareness. If sleep ensues before the interview is well under way, it is wise to give the caffeine intravenously or subcutaneously to quicken the awakening so that the interview may be carried on without undue delay. Remember, it is imperative to have a stimulant on hand for instantaneous use. Do not compromise this principle.

It is well to have a quiet room, dimly lit and empty, except for the bed and a chair or two. This affords better protection for the patient, if you stir up a violent combat reaction. The patient should not have any breakable object on his person, and it is preferable to have him dressed in pajamas. It is assumed that some time has been spent beforehand in developing confidence and understanding of the purposes of the treatment. The better the relationship between the patient and the doctor the more frequently and more readily one will obtain effective results. The skillful use of suggestion makes a great difference. One should be well acquainted with the routine techniques of hypnosis, and one should repeat with confidence a number of suggestions directed toward relaxation and sleep.

These suggestions should be made so that they will fit in with the background of the patient's understanding and personality. Occasionally this will not apply to very hostile and resistive patients. For this type of patient the amytal session may be the quicker and more effective way to erase the barriers to deeper understanding and control of unbridled aggression.

The sodium amytal should be administered very slowly, more slowly than at the rate of 1 gr. per minute. During the administration of the drug it is well to begin with neutral topics regarding the past life of the patient and gradually to work into the military history. When the patient begins to speak more freely or in a mush-mouthed manner, then it is well to try to stimulate a return to combat by using alert signals ("condition red, blasts on a siren, etc.") and by strong and repeated suggestions that the patient is "on the line" in the area of his most severe combat experience ("hill 69, bloody knoll," etc.). Set up a combat situation, and try to get the patient to go through the commands and action of the day, taking the rôle of the persons to whom he calls for help or advice. This means that you must have an acquaintance with military terminology, slang and the local ground rules in the combat area from which the patient has come. This is best obtained in previous interviews with the patient wherein you will learn of the alert signals, the areas of the toughest action, the names of his subordinates and his superiors, the location of the command post and the patient's rôle in the action.

If this does not strike a response, then it is well to systematically explore the immediate situation and complaints, trying to trace their origins and relationship to the past. In this connection it is invaluable to stimulate a recall of dreams and recent phantasies. The recent dreams are very productive of clearer insights into forgotten traumatic events, conflicts, and so forth. It is relatively simple to allow the patient to make associations with the content of the dream and to aid him in pointing toward the meaning of such dreams.

The therapist's skill in dramatizing the combat situations may determine the richness of the interview. Battle records, simulated alert signals and so forth will help to strike action from the patient. Even when the events of combat have not been emotionally upsetting, it is possible to have the patient relive the experiences of the line; we have observed the work of some outstanding combat men as they go through an action and direct the men under them with precision and coolness.

Except with combat cases, there is little need to deviate from the routine skills and techniques of interviewing. However, it is well to *save the more delicate probing for the later stages of the interview when you are assured of a deep "sleep."* For example, when you are trying to determine the validity of hallucinatory material it is well to wait until a deep level of "sleep" is achieved before direct questions are given. However, under narcosis it is easier to go directly to the tender areas or the forgotten episodes by pointed questioning.

The depth of narcosis is difficult to determine, and one learns when to stop the administration of the drug by experience. Soon one learns to appreciate a sudden relaxation, a lid-flickering, slower and more regular breathing, a more rapid flow of ideas and a quicker response to questioning. Skill in knowing when to stop is important, for it is easy to get too deep a level of narcosis. It is well to administer the drug very slowly in the beginning of one's experience and to continue with the interview from the

beginning to the end of the injection. Be ever alert for changes in muscle tension, the cessation of a tremor, the absence of blocking, and so forth. These signs are valuable indicators of when to stop giving the drug. If in doubt, it is easy to try some direct suggestions and to note the effect. If narcosis is not deep enough, you will readily observe it.

It has been our experience that much more of the drug is needed for a very hostile or resentful patient and that it is not unusual for us to give from 8 to 10 gr. of sodium amytal to get proper relaxation and narcosis with resistive subjects. In fact, it has been our experience that the amount of drug administered is a good index of the amount of resistance toward narcosis. It is surprising how bitter and resentful subjects may resist the effects of amytal. This is particularly true when you are using the method in legal work with criminals. Then, too, we did not begin to get effective results with conversion symptoms until we began to use larger doses, that is, above $7\frac{1}{2}$ gr., and now we are convinced that resistance is a good antidote and that you should slowly push the medication until the desired level of narcosis is reached, regardless of the amount needed. To date, we have not exceeded 15 gr. and have only rarely had to use that much. Only 1 case of respiratory arrest has been observed in the treatment of over 500 cases, and this was after the giving of less than 4 gr. of sodium amytal. This was a patient unusually susceptible to the narcotic effect, and we had given the medication too rapidly. However, the administration of 15 gr. of caffeine intravenously was followed by a prompt return of respiration.

Tension and resistance seems to raise the threshold to narcotic effects like pain raises the threshold to morphine effect. Furthermore, it is precisely with cases that do exhibit marked resistance and tension that amytal proves often more effective than other less direct approaches to treatment.

We have made no tabulations of results with the use of amytal narcosis in the treatment of our cases. Yet we have, over the last year, obtained certain definite impressions regarding the value of this therapeutic approach. The technique is valuable in relatively unskilled hands, and training in the usage of the amytal interviews is a relatively simple task. Furthermore, amytal is more widely effective when it is given in sufficient quantities to produce appreciable clouding of consciousness and thickness of speech.

As a beginning for the discussion of the values of the amytal interview it may be well to list some of the effective applications:

1. Recovery of forgotten or painful experiences and conflicts.
2. Reliving of emotionally traumatic experience.
3. Aid in differential diagnosis.
4. Treatment of hostile and resentful patients.
5. Uncovering faking and conscious distortions.
6. Uncovering hallucinatory material.
7. Treatment of conversion symptoms (limps, backaches and so forth).
8. Facilitate hypnotic treatments.
9. Control of excitements, panics and rage reactions.
10. Clarification of amnesic episodes.
11. Treatment of mute or catatonic patients.
12. Correction and clarification of psychogenic components of structural disorders:
    (*a*) Orthopedic problems.
    (*b*) Post-traumatic head syndromes.

13. Aid in legal psychiatric work:
    (*a*) Questioning of suspected thieves, and so forth.
    (*b*) Questioning regarding facts in self-mutilation.
    (*c*) Clarification of so-called "AWOL or drunken amnesias."
14. Aid in re-testing when conscious distortions or inadequate coöperation is suspected:
    (*a*) Intelligence testing.
    (*b*) Rorschach testing.

The amytal interview is very effective as therapy for combat cases of relatively recent origin, for recovery of forgotten or painful battle experience and for the reliving of the emotionally traumatic situations. It helps very much in establishing a firm basis for effective therapy and interpretation. We think that the reliving of the emotional experiences is beneficial, and we have observed that battle dreams, sleeplessness, irritability, associability and negativistic reactions subside promptly after an effective treatment. The more lasting effects can be established by interpretation of this material during the next 2 or 3 days following the treatment. The amytal interviews should be repeated until one attains a much quieter reaction or observes no marked emotionally tinged battle experiences like the ones observed at the first or second treatment. More often it has been true that only 2 or 3 treatments are necessary as long as they are followed through by careful interpretation and elaboration of the material when the patient is alert.

The differential diagnosis of schizophrenic reactions is facilitated by amytal sessions. On a number of occasions we have been able to demonstrate hallucinatory material that had been present but not revealed during the earlier days of hospitalization. Then, too, we have observed questionable psychotic reactions where the facts have been much clearer under amytal. For example, one prisoner who attempted to imitate an acute psychotic episode that had been observed by him during a previous prison stay admitted the falsification under amytal. Furthermore, where one has some local structural damage with a functional overlay, it is very helpful to give amytal to evaluate the amount of structural and functional disability. From this evaluation one may proceed to make a more direct interpretation of the functional elements.

Also, resentful and negativistic patients respond to amytal sessions given within the first day or two of admission and thereby reduce the time necessary for developing a clearer understanding of the origins of the hostility and resentfulness. These patients need a much larger dose of sodium amytal. Occasional striking results have been obtained from prompt use of amytal interviews for this type of reaction. Likewise, the same approach has given great help with mute and catatonic patients and has facilitated the ward management of that type of case.

A correlated problem deals with patients who claim that they cannot speak English, particularly Mexican patients. Under amytal one may be able to demonstrate a much better grasp of English. Likewise, where we have clinically estimated a greater intelligence than was demonstrated through intelligence testing, we have at times been able to get a more reliable estimation under amytal. This applies to other types of tests like the Rorschach and the Shipley-Hartford Retreat Scale. It is simple to repeat a test during an amytal interview when the examiner is unsatisfied with the productivity of the patient during the wakeful state.

We had 4 or 5 cases of malingering where we have been able to demonstrate this conscious faking during the amytal sessions. It is our impres-

sion that sodium amytal interviews are particularly valuable where faking or conscious distortions are suspected.

The use of amytal sessions in the treatment of conversion symptoms has been described before. We find it particularly helpful in demonstrating functional limps and backaches, but our results have been erratic. With the Negro patients we have had very poor results. With a few of the intelligent white patients we have had rather prompt recoveries and have been able to interpret the meaning of the conversions to the patient within a short time.

It is obvious that sodium amytal can be used in the control of excitements, panics and rage reactions, like any sedative. However, it would be wiser to give the amytal intramuscularly instead of trying to struggle with the patient to give an intravenous dosage. The use of sodium amytal in the recovery of amnesic episodes has been previously described, and its use is valuable for cases that show extensive amnesias.

Skill in the use of amytal is a necessary art in the adequate practice of military psychiatry, and one may attain this skill by using the method sufficiently to become acquainted with effects and results upon patients well known to the doctor. Skill in the use of amytal or a similar agent will provide the therapist with another valuable and rapid type of treatment and diagnostic agent.

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## PHYSIOLOGY

PROCEEDINGS OF
THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA
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**The Necessity of Fluorine in the Diet of the Rat.*** J. F. McClendon and Wm. C. Foster (Dept. of Physiology, Hahnemann Med. Coll.). Since

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all foodstuffs we analyzed contained fluorine, we used fluorine-free corn, sunflowers, soy beans and yeast grown by hydroponics. To avoid the fluorine in city air, a greenhouse was built on Trooper Road. Traces of fluorine in rain water from a glass roof were removed by acid exchange resin, amberlite IR4. Fluorine was removed from reagent nutrient salts by making a stock solution about pH 12 and before more than 10% of the calcium phosphate precipitated filtering by suction into enough fluorine-free sulfuric acid to bring the pH to 4.5 and diluting to prevent the precipitation of gypsum. The solutions were analyzed often and air pumped to the roots. Two rats, which had just been weaned, on this diet were dying in 48 days but 1 was revived with fluorine-containing milk and died in 70 days. The addition of 1% calcium citrate containing 0.4 ppm. fluorine improved the health of 5 other rats on this diet. One was killed at 56 days, 1 at 70 days and 3 are living at 74 days. Since rats in the wild state do not have mineral supplements and all calcium salts seem to be made from CaO containing 4 to 6 ppm. fluorine which accompanies the calcium through purification processes, we think the diet without additional calcium justified. Soy beans contain 0.25% calcium and sunflower seeds 0.2%. Fluorine is passed from mother to offspring and the less fluorine in the mother's diet, the fewer young are born and the less is the milk supply of the mother. All these rats had extensive decay of the molar teeth; in some cases all of the crowns were lost.

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**Somatic Factors in Electroencephalography.** T. Cunliffe Barnes (Dept. of Physiology, Hahnemann Med. Coll. and Hosp. of Phila.). In 46 persons, 28 gave abnormal delta EEGs in overventilation; 18 had good vital capacities and 10 poor. In the 18 that gave normal EEGs in overventilation, 13 had poor and only 5 had good vital capacities. A good vital capacity produces sufficient hypocapnia to slow the EEG. Of 22 army medical students, 11 had 90 to 130 mg. per 100 cc. blood sugar (non-fasting), and most showed abnormal overventilation EEGs, while 11 with levels of 130 to 160 had few abnormal waves in overventilation EEGs. Blood sugar enables the brain to withstand the vasoconstriction of hypocapnia. In 23 persons with abnormal overventilation EEGs, the pulse rose 26 beats per min. (average), while in 10 with normal overventilation EEGs, the pulse rise was only 15 beats. In 11 cases with abnormal overventilation EEGs, the skin temperature (thumb) fell 1.7° C. (average), and in 6 cases with normal overventilation EEGs the skin temperature rose 0.2° C. The rising pulse and cooling skin indicates sympathetic vasoconstriction producing slow ischemic EEGs in deep breathing, which may be overcome by a strong parasympathetic component. Of 15 regular breathers, 13 had low alpha waves in occipital lobes (visual imagery) in contrast to 12 irregular breathers (laryngeal component of auditory imagery) who had inactive visual centers (alpha over 70%).

Fourteen schizophrenics had an average alpha index of 23% (5 had no alpha), 10 manics had alpha index of 44% (1 had no alpha). Of 25 schizophrenics, 16 had regular pneumogram and 10 of 21 manics had regular breathing. The depth of the breathing recorded by a Marey tambour gave the most striking difference—3 mm. for schizophrenics and 9 mm. for manics. A regular, very shallow pneumographic record seems characteristic of dementia præcox except during violent hallucinations. Seven of 9 schizophrenics with auditory hallucinations had irregular pneumograms (as predicted from normals).

Brain waves are taken to be phase-boundary potentials produced by acetylcholine. Benzyl alcohol (inactive with acetylcholine) containing 37% fresh human cortex generates 12 mv. negative with 0.05% acetylcholine (in Dr. Beutner's oil-cell).

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**Experience With Mild Exercise as a Test for the Convalescent State.*** Isaac Starr, R. Mayock and M. G. Battles (Hartzell Research Dept. of Therapeutics and Harrison Dept. of Surgical Research, Univ. of Penna.). By means of a standard exercise test, lifting a 10 pound iron bar from the chest to arms length above it, we have sought to demonstrate physiologic abnormalities during convalescence from surgical procedures.

Oxygen consumption and volume and rate of respiration have been determined before, during, and after standard exercise. Cardiac output (ballistocardiogram) and pulse rate were estimated before, just after, and 5 minutes after the same standard exercise.

Measurement of the *amount* of the changes induced by the exercise revealed no significant differences which could be attributed to convalescence. However, when attention was given to the duration of the changes induced by the exercise, the averages showed significant differences, the increased oxygen consumption, respiration, and pulse rate declining to the resting level more slowly during convalescence than before operation.

The resting respiration and oxygen consumption were not significantly changed during convalescence.

The variability in the physiologic response to exercise was so large that a test of the type used gives no promise of providing a satisfactory measure of the duration of convalescence in individual cases. However, the slow return to normal of pulse rate, respiration, and oxygen consumption after exercise is over may have some value as an indication of persisting abnormality in certain individuals and will provide significant differences when data obtained from a series of 10 or more cases are averaged.

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**Dietary Requirements for Nitrogen Equilibrium in the Period Immediately Following Certain Major Surgical Operations.*** C. Riegel, J. E. Rhoads, C. E. Koop, R. P. Grigger, L. Bullitt and D. Barrus (Harrison Dept. of Surgical Research, Univ. of Penna.). Surgical patients kept on the usual hospital régime following gastric and cranial operations were found to be in negative nitrogen balance during the first 5 postoperative days. By placing such patients on a diet by mouth or Abbott-Rawson tube containing approximately 0.25 gm. nitrogen and 25 calories per kilogram daily, or over, a majority could be brought into positive nitrogen balance. The types of food used were: (1) regular mixed house diet, (2) Amigen (Mead Johnson & Co.), (3) Amigen plus house diet, (4) gastrostomy mixture (milk, skim milk powder, egg, cottage cheese, soy bean flour) and (5) lactalbumin hydrolysate. Both hydrolyzed protein and whole protein at this level were equally effective.

Patients fed intravenously at this same level with gelatin alone or Amigen alone were in negative nitrogen balance, suggesting that intravenous feeding is perhaps not as effective as tube feeding.

Plasma protein concentration often increased when patients were given

* Work done under contract with the Office of Scientific Research and Development.

special feeding, even though they were not given over 0.25 gm. nitrogen and 25 calories per kilogram or were not in nitrogen equilibrium.

Weight loss in patients on diets of 0.25 gm. nitrogen and 25 calories per kilogram daily was less than in those patients kept on the usual hospital régime.

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**The Effect of Ultra-violet Irradiation on the Toxicity and Chemotherapeutic Action of Stilbamidine.** L. D. SEAGER, G. R. WELLS, and GINA CASTELNUOVO (Depts. of Pharmacology and Anatomy, Woman's Med. Coll. of Penna.). Solutions of the various salts of stilbamidine are fluorescent. On irradiation by ultra-violet light this property is altered and, as shown by Fulton and Yorke, the toxicity for mice is increased 6 to 8 times. According to Henry, some of the stilbamidine is changed from the trans to the cis form and some is changed to 1, 2, 4, 5 tetra (4 amidino phenyl) cyclobutane. In experiments on dogs we have found that the irradiated compound produces a greater fall in blood pressure than the non-irradiated drug. In 5 dogs the dosage of the irradiated solution was altered until equivalent changes in pressure were produced to those of a standard dose of the non-irradiated drug. The depressor effect was potentiated 3 to 4 times. With equal falls in pressure however, the irradiated solution gave a more prolonged depressor effect. Mice inoculated with *T. equiperdum*, 1,000,000 per kg., were treated with varying doses of the irradiated and the non-irradiated compounds. The agents were given orally 3 times daily for 4 days. The ED 50 for bringing about the cure of the infection was between 1 and 1.2 mg. per kg. for the normal drug, and between 3 and 4 mg. per kg. for the irradiated solution. Boiling solutions of the drug for 2 hours did not alter its toxic or therapeutic properties. It is apparent that irradiation increases the toxicity of stilbamidine 3 and 4 times, but reduces its chemotherapeutic effect to a similar extent.

# BOOK REVIEWS AND NOTICES

AN INTRODUCTION TO SOMATIC METHODS OF TREATMENT IN PSYCHIATRY. By WILLIAM SARGANT, M.A., M.B. (CANTAB.), M.R.C.P., D.P.M., Medical Officer, Maudsley Hosp., and ELIOT SLATER, M.A., M.D. (CANTAB.), M.R.C.P., D.P.M., Medical Officer, Maudsley Hosp. Pp. 171. Balt.: Williams & Wilkins, 1944. Price, $2.50.

IN this book is found a battery of physiochemical therapies for the psychoses—insulin and electric shocks, continuous sedations, vitamins and endocrines and others. On one hand these procedures link psychiatry with general medicine; on the other they fight the great discourager in psychiatry—chronicity.

The chapter on insulin shock is detailed and trustworthy. The remarks on depth of stupor and treatment of prolonged stupor should be followed by a reading of 1944 articles by Himerich and Rivers and Rome, which go more deeply into the subject. The various treatments of the epilepsies make an interesting section because of the new suggestions and controls opened up by the electro-encephalograph. The authors put a discussion of psychotherapy as a help to somatic means in a final short chapter.

This is a sound, stimulating book for the beginner in psychiatry. There is no bibliography. E. B.

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MANUAL OF TROPICAL MEDICINE. Prepared under the Auspices of the Division of Medical Sciences of the National Research Council. By COL. THOMAS T. MACKIE, M.C., A.U.S. (and 8 others). Pp. 727; 287 ills., 6 in color. Phila.: Saunders, 1945.

THIS is an excellent example of printing and binding; but, as a presentation of the essentials of Tropical Medicine, it leaves something to be desired. Not that it does not contain essentials and more, as indicated by the following chapter headings: The Viruses, Rickettsial Diseases, Spirochetal Diseases, Bacterial Diseases, Protozoal Diseases, Helminthic Diseases, Nutritional Diseases, Miscellaneous Conditions, Medically Important Arthropods and Laboratory Diagnostic Methods. The "Miscellaneous Conditions" are Bartonellosis, Tropical Ulcer, Desert Sore, Cutaneous Diphtheria, Granuloma Inguinale; Scabies, Effects of Heart, and Certain Medically Important Animals. The general plan of the book is said to be more or less the same as the course in Tropical and Military Medicine as presented by the authors and their colleagues at the Army Medical School. All of this is excellent and so are the many photographs and charts which illustrate the book; but the text is not well written. In fact it makes unnecessarily difficult reading. This is not only my opinion but also that expressed by undergraduate medical students to whom the book had been assigned. These might not be regarded as major faults in the discussion, but lack of coherence in one place or wordiness in another can only discourage an overworked student. The text hardly justifies the title "A Manual of Tropical Medicine." H. R.

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ON MODERN SYPHILOTHERAPY WITH PARTICULAR REFERENCE TO SALVARSAN. By ALBERT NEISSER. Translated by ISABELLE VON SAZENHOFEN WARTENBERG. Pp. 42. Balt.: Johns Hopkins Press, 1945. Price, $1.00.

THIS reprint from *The Bulletin of the History of Medicine* (**16**, 469, 1944) contains a biography of Albert Neisser and a bibliography of his works by Frances Tomlinson Gardner, together with a translation by Isabelle von Sazen-

hofen Wartenberg, of his article, "On Modern Syphilotherapy With Particular Reference to Salvarsan."

J. E. Moore has recently (*Am. J. Syph., Gonor. and Ven. Dis.*, **29**, 185, 1945) stated that "the chemotherapy of syphilis is divisible into three periods of very unequal length: the first lasting 410 years, from 1493 to 1903; the second 40 years, from 1903 to 1943; the last, in which the doors of knowledge have as yet opened only a tiny crack, for 16 months, from June 1943 to the present moment." Now that we are in the midst of the third—penicillin era—it is refreshing to read a first-hand presentation of principles by one of the pioneers of the second period which up to now has been called "modern" syphilology. The content of Neisser's dissertation is very timely, as experience with penicillin is emphasizing more and more that many of the facts he stressed, prolongation of treatment, combined treatment, and so forth, are applicable to effective penicillin therapy of syphilis.

The biographer has given a sympathetic and touching sketch of Neisser, and the bibliography indicates the range of his busy scientific life.

The book, considering wartime restrictions, is attractively presented. The Reviewer believes everyone interested in syphilology should read this volume.

H. B.

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TROPICAL MEDICINE. By SIR LEONARD ROGERS, K.C.S.I., C.I.E., LL.D., M.D., B.S., F.R.C.P., F.R.C.S., F.R.S., Major-General, I. M. S., Ret., Physician and Lecturer, Lond. School of Trop. Med.; Lecturer on Trop. Med., Lond. School of Med. for Women; Late Professor of Pathology, Medical Coll., Calcutta; and SIR JOHN W. D. MEGAW, K.C.I.E., B.A., M.B., HON. D.Sc. (Queen's Univ., Belfast), Major-General, I. M. S., Ret., Late Lecturer, Lond. School of Trop. Med.; Director-General, Indian Med. Serv.; and Director and Professor of Trop. Med., Calcutta School of Trop. Med. and Hyg. 5th Ed. Pp. 518; 2 colored plates and 87 text-figures. Baltimore: Williams & Wilkins, 1944.

The 5th edition of this book in less than 15 years speaks for itself. It also reflects well the high places of the authors in the field of Tropical Medicine. Not only is this book a product of long personal experience both in teaching and research, but, equally important, it is well written. Of the illustrations (charts and maps), the charts which portray insect-borne disease are especially good. They combine the development of pathogens in the vectors with the story of the diseases in man, giving the time in days required for the vector to become infective, the fate of the organism in the vector, incubation period for man, mode of onset, temperature curve and other distinctive changes. Directions for treatment reflect the views and background of the authors and could have been presented more effectively by tabulation. In this respect it may be noted that quinacrine (atabrine) does not receive the place it deserves in the therapy of malaria. There are other examples of conservatism in the book, but these do not lessen its value. It can be recommended as a brief but adequate discussion of Tropical Medicine. H. R.

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OUTLINE OF THE AMINO ACIDS AND PROTEINS. By MELVILLE SAHYUN, M.D., PH.D., Vice-President and Director of Research, Frederick Stearns & Co. With 13 contributing authors. Pp. 251. New York: Reinhold Pub. Corp., 1944. Price, $4.00.

INTEREST in problems dealing with proteins and amino acids has developed widely in many fields of biologic and medical sciences. Students will find this book of particular interest for its presentation of the elements of the chemistry and biochemistry of the amino acids and proteins in a simple, readable manner.

The subject is presented in 12 chapters by qualified contributing authors: Discovery of the Amino Acids (Melville Sahyun); Occurrence, Amino Acid Content and Properties (C. L. A. Schmidt); Protein Structure (H. B. Bull);

Hydrolysis of Proteins (Melville Sahyun); Synthesis and Isolation of Certain Amino Acids (H. E. Carter and I. R. Hooper); Methods of Analysis for Amino Acids and Proteins (D. M. Greenberg); Relation of Amino Acids and Their Derivatives to Immunity (Michael Heidelberger); Relation of Amino Acids to Biologically Important Products and the Rôle of Certain Amino Acids in Detoxication (A. J. Quick); Metabolism of Proteins and Amino Acids (W. M. Cahill); Intermediary Metabolism of Individual Amino Acids (W. M. Cahill); Nitrogen Equilibrium and the Biological Value of Protein (W. M. Cahill and A. H. Smith); Amino Acids and Proteins in Nutrition (Madelyn Womack and C. F. Kade).

Approximately half of the book is concerned with fundamental chemistry of the amino acids and proteins; the remainder is devoted to biochemistry and metabolism. There is considerable duplication in the information presented in the last 5 chapters, as can be predicted from the titles of the chapters. Adequate bibliographic references to current literature are appended to each chapter, and an appendix lists U. S. patents issued on amino acids and related organic compounds. H. V.

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THE ETIOLOGY, DIAGNOSIS, AND TREATMENT OF AMEBIASIS. By CHARLES FRANKLIN CRAIG, M.D., M.A. (HON.), F.A.C.S., F.A.C.P., Col., U.S.A., Retired, D.S.M.

AMEBIASIS and amebic dysentery are as widespread as fecal contamination of food and drink. This is an established fact of many years standing, but so often is it overlooked or forgotten that it might just as well be a new discovery. Explanation of this state of affairs is not difficult. First, textbooks published in the United States commonly draw on material from North China, the Philippines or Panama. Thus *Endamœba histolytica* comes to be associated with the tropics or with poorly sanitated regions of the Orient. With little more effort, authors might just as well illustrate their texts with cases that are buried in the records of every northern hospital of any size. Another and perhaps more important block to recognition of clinical cases of amebiasis is microscopic examination of feces. This is a difficult and unpleasant task. It cannot be trusted to the average laboratory technician, and, until it may be or until the "higher brass" may be persuaded to accept this responsibility, the great majority of cases of amebiasis will pass undiagnosed. Fortunately most of them tend to be relatively mild.

More than any other American author Colonel Craig has attempted to stimulate justifiable interest in amebiasis in this country. In numerous papers and addresses he has discussed epidemiology, diagnosis and treatment and in 1934 Charles C Thomas published his monograph "Amœbiasis and Amœbic Dysentery." This book under review is essentially a revision of this monograph. It is an up-to-date consideration of infection by *Endamœba histolytica* and, if it receive the attention which it and this infection warrant, fewer cases of amebiasis and amebic dysentery will go undiagnosed.

H. R.

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PATHOLOGY of LABOR, THE PUERPERIUM AND THE NEWBORN. By CHARLES O. MCCORMICK, A.B., M.D., F.A.C.S., Clinical Professor of Obstetrics, Indiana Univ. School of Medicine; Consulting Obstetrician to William H. Coleman Hosp. for Women, Indianapolis City Hosp. and Sunny Side Sanitarium. Pp. 399; 191 figs. St. Louis: Mosby, 1944. Price, $7.50.

THIS volume is based upon the author's lectures prepared for senior medical students. The material is presented in the form of a synopsis, arranged with numerous paragraph headings, and the majority of the facts are arranged numerically. Its condensed form makes it ideal as a means for preparing for examinations. The disadvantage of such a form of preparation lies in the fact that it tends to place a premium on memorizing. D. M.

DUODENAL AND JEJUNAL PEPTIC ULCER. By RUDOLF NISSEN, M.D., Attending Surgeon, Jewish Hosp. of Brooklyn; Member, Medical Advisory Board, National Jewish Hosp. of Denver; Formerly Professor of Surgery and Head of Department of Surgery, Univ. of Istanbul; and Associate Professor of Surgery, Univ. of Berlin. Pp. 143; 123 figures. New York: Grune & Stratton, 1945. Price, $4.75.

THIS book deals with the surgical technique of gastro-duodenal resections for duodenal ulcer. It is adapted for those engaged in gastric surgery.

The first part presents the various techniques of resection for duodenal ulcer along with an evaluation of the results to be expected. The author includes his own technique of resection and closure of the duodenal stump in penetrating ulcers of the posterior duodenal wall. The second part is devoted to the technique of resection of postoperative marginal ulcers and fistulas. A 2-stage operation is presented for poor risk patients.

The book is well illustrated, and the subject matter is clearly presented. It should be of value to all who are concerned with the technical aspects of surgery of ulcers and particularly with the more complicated problems for which secondary operations are required. R. P.

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THE NEW YORK HOSPITAL. A History of the Psychiatric Service (1771–1936). By WILLIAM LOGIE RUSSELL, Professor of Psychiatry, Emeritus, Cornell Univ. Medical Coll.; Consulting Psychiatrist, New York Hosp. Pp. 556. New York: Columbia Univ. Press, 1945. Price, $7.50.

As is stated on the cover, "this work gives an account of the earliest, and for almost 50 years, the only provision for the hospital treatment of the mentally ill in the state of New York. The project was instituted in 1771, by a small group of physicians and other private citizens in connection with the establishment of a general service and teaching hospital in New York City . . . . Physicians, nurses, hospital managers, and others officially concerned with the problems of mental illness will find encouragement and guidance in the experiences related. In addition, this intimate account of the development of a well-controlled and liberally supported service will be useful to teachers and students of psychiatry and mental hygiene and to those interested in social history and organization, New York history, the history of psychiatric nursing education, and public welfare."

This book is naturally of special interest to those connected with the New York Hospital and those interested in psychiatric hospitals. As a publicly available record, the advantage of such detailed local histories so greatly out weighs the occasional, unavoidable tedium of the story, that the matter does not seem to require further argument—the more such good local productions the better! E. K.

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WOMEN AND MEN. By AMRAM SCHEINFELD, Author of "You and Heredity." Pp. 453. Illustrations by the Author. New York: Harcourt, Brace, 1944. Price, $3.50.

THIS book in semi-popular style by an experienced writer in the field aims to help the two sexes understand themselves in relation to each other. The author first touches on Myths and Muddles arising from failures in understanding, then in the other 29 chapters, he pursues his theme of basic sex differences in logical order: first the seed, then first steps and puberty, with emphasis on the earliest years when developing sex differences are most significant; sickness; sex life; crime; labor, and so forth to the "marriage of tomorrow." Added to evidence of the lesser rôle of the male in procreation, he has added instances of greater female power of non-muscular kinds and of persistence in each sex of bisexual characteristics, all leading to the more important place occupied by woman in modern life. This same well-informed exposition of the overlapping behavior patterns of the two sexes should be profitable to the physician as well as to the discerning lay man. E. K.

THE CHEMISTRY AND PHYSIOLOGY OF HORMONES. Publication of the American Association for the Advancement of Science. Edited by FOREST RAY MOULTON. Pp. 243. Washington, D. C.: American Assn. Advanc. of Sci., 1944. Price, $3.50 ($4.00).

THIS is a Symposium volume of 17 papers presented during a 5 days, Research Conference at Gibson Island, Md., during 1943. The papers are reviews that were presented by selected active research workers, with modifications made as a result of discussions that ensued among those attending the conference. There are many charts and illustrations. Over 200 references are combined at the end of the book.

As a compilation of data and expression of modern concepts of the chemistry and physiology of hormones, the book presents desirable authoritative information about research aspects of endocrinology.

The pituitary receives greatest emphasis, the parathyroids are entirely omitted. I. Z.

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## NEW BOOKS

*Penicillin and Other Antibiotic Agents.* By WALLACE E. HERRELL, M.D., M.S., F.A.C.P., Assistant Professor of Medicine, the Mayo Foundation, Univ. of Minnesota; Consultant in Medicine, Mayo Clinic, Rochester, Minn. Pp. 348; 45 figs.; 45 tables. Phila.: Saunders, 1945. Price, $5.00.

*Transactions of the Association of American Physicians.* Fifty-eighth Session Held at Atlantic City, N. J., May 9, 1944. Vol. LVIII. Pp. 204. Phila.: Assn. of Am. Phys., 1944.

*Foster Home Care for Mental Patients.* By HESTER B. CRUTCHER, Director of Social Work, State of New York, Department of Mental Hygiene. Pp. 199. New York: Commonwealth Fund, 1944. Price, $2.00.

*Fundamentals of Pharmacology.* By CLINTON H. THIENES, M.D., PH.D., Professor and Head of the Department of Pharmacology, School of Medicine, Univ. of Southern California. Pp. 497. New York: Hoeber, 1945. Price, $5.75.

*The Psychology of Women.* A Psychoanalytic Interpretation. Vol. II. Motherhood. By HELENE DEUTSCH, M.D., Associate Psychiatrist, Massachusetts General Hosp.; Lecturer, Boston Psychoanalytic Institute. Pp. 399. New York: Grune & Stratton, 1945. Price, $4.50.

*Modern Psychiatry.* By WILLIAM S. SADLER, M.D., F.A.P.A., Consulting Psychiatrist to Columbus Hosp.; Consultant in Psychiatry, The W. K. Kellogg Foundation; Fellow of the American Psychiatric Assn.; Member of the American Psychopathologic Assn. Pp. 896. St. Louis: Mosby, 1945. Price, $10.00.

*Ageing and Degenerative Diseases.* Edited by ROBERT A. MOORE, School of Medicine, Washington Univ. Vol. XI of Biological Symposia. A series of Volumes Devoted to Current Symposia in the Field of Biology. Edited by JAQUES CATTELL. Pp. 242. Various tables and figs. Lancaster: Cattell Press, 1945. Price, $3.00.

*Francois Magendie.* Pioneer in Experimental Physiology and Scientific Medicine in XIX Century France. By J. M. D. OLMSTED, Professor of Physiology, Univ. of California. With a Preface by JOHN F. FULTON. Illustrated. Pp. 290. New York: Schuman's, 1944. Price, $5.00.

*The Chemical Formulary.* A Collection of Valuable, Timely, Practical Commercial Formulæ and Recipes for Making Thousands of Products in Many Fields of Industry. Vol. VII. Editor-in-Chief, H. BENNETT. Pp. 474. Brooklyn: Chemical Publishing Co., 1945. Price, $6.00.

*Malaria, Primate.* By S. D. ABERLE, M.D. National Research Council, Division of Medical Sciences. Pp. 171. Issued by the Office of Medical Information (Under grant of the Johnson & Johnson Research Foundation), March, 1945.

*Public Medical Care.* Principles and Problems. By FRANZ GOLDMANN, M.D. Pp. 226. New York: Columbia Univ. Press, 1945. Price, $2.75.

## NEW EDITIONS

*Diseases of the Nervous System in Infancy, Childhood, and Adolescence.* By FRANK R. FORD, M.D., Associate Professor of Neurology, The Johns Hopkins Univ. Second Ed. Pp. 1143; 164 ills., 22 charts, 14 tables. Springfield: Thomas, 1944. Price, $12.50.

*Infants and Children.* Their Feeding and Growth. By FREDERIC H. BARTLETT, M.D., Attending Pediatrician, Babies' Hosp., New York City. New Ed. Pp. 428. New York: Farrar & Rinehart, 1944. Price, $2.00.

*Essentials of Body Mechanics in Health and Disease.* By JOEL E. GOLDTHWAIT, M.D., F.A.C.S., LL.D., *et al.* With a Chapter on the Heart and Circulation as Related to Body Mechanics, by WILLIAM J. KERR, M.D., F.A.C.P. Pp. 337: 128 ills. Fourth Ed. Phila.: Lippincott, 1945. Price, $5.00.

*Dietary of Health and Disease.* By GERTRUDE I. THOMAS, Assistant Professor of Dietetics, Univ. of Minnesota. Fourth Ed. Pp. 308; illustrated. Phila.: Lea & Febiger, 1945. Price, $3.50.

*The Management of Obstetric Difficulties.* By PAUL TITUS, M.D., Obstetrician and Gynecologist to the St. Margaret Memorial Hosp., Pittsburgh; Secretary of the American Board of Obstetrics and Gynecology; Commander (MC), USNR, attached to Professional Division, Bureau of Medicine and Surgery, Navy Department, Washington, D. C. Third Ed. Pp. 1000; 426 ills. and 8 color plates. St. Louis: C. V. Mosby, 1945. Price, $10.00.

*The Human Mind.* By KARL A. MENNINGER. Third Ed. Pp. 517; corrected, enlarged and rewritten. New York: Knopf, 1945. Price, $5.00.

*The Basis of Clinical Neurology.* The Anatomy and Physiology of the Nervous System in Their Application to Clinical Neurology. By SAMUEL BROCK, M.D., Professor of Neurology, Coll. of Medicine, New York Univ. Second Ed. Pp. 393; 72 figs. Baltimore: Williams & Wilkins, 1945. Price, $5.50.

*A Synopsis of Medicine.* By SIR HENRY LETHEBY TIDY, K.B.E., M.A., M.D., B.Ch. (OXON.), F.R.C.P. (LOND.), Extra Physician to H. M. The King; Consulting Physician to St. Thomas's Hosp. Eighth Ed., revised and enlarged. Pp. 1215. Baltimore: Williams & Wilkins, 1945. Price, $7.50.

*Textbook of Neuropathology.* By ARTHUR WEIL, M.D., Associate Professor of Neuropathology, Northwestern Univ. Med. School. Second Ed. Pp. 370; 289 ills. New York: Grune & Stratton, 1945. Price, $5.50.

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